Clinical

Biochemistry

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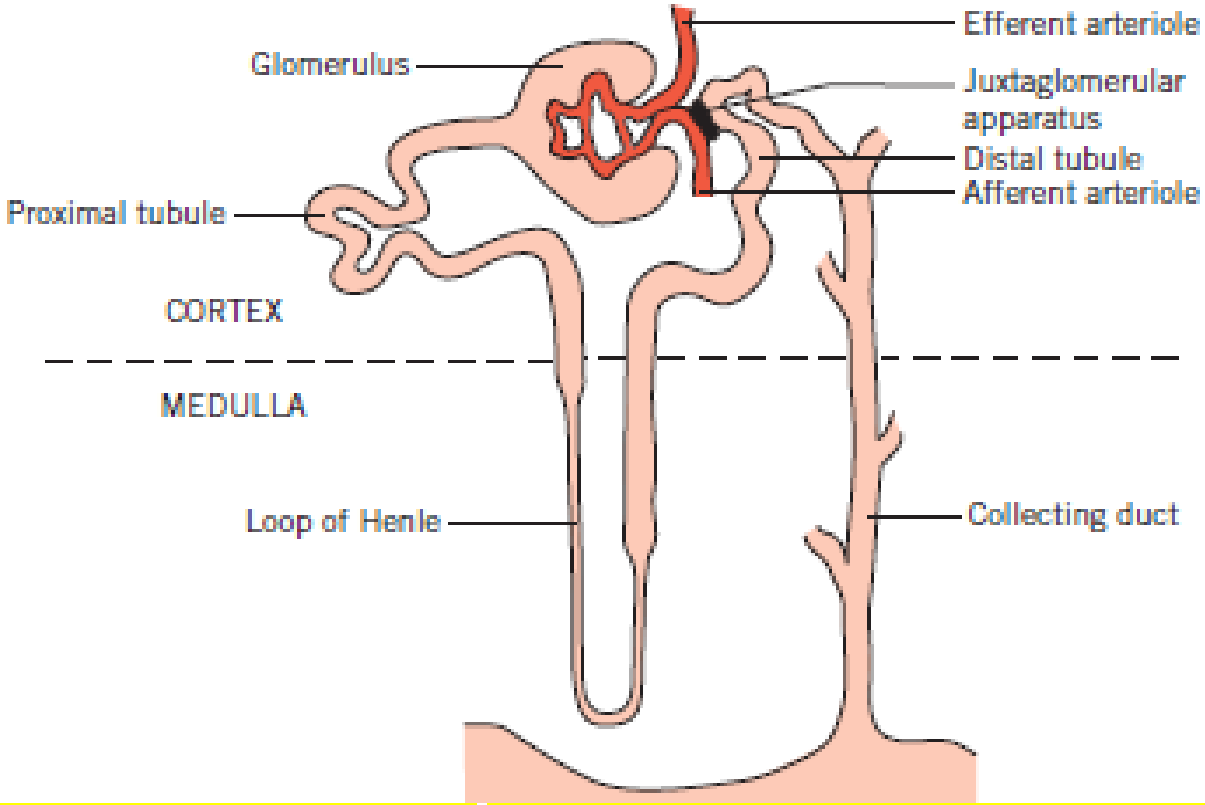
Chapter 1
The kidneys

- The kidneys excrete metabolic waste products, and have an essential homeostatic function
- **they control** the body solute and water status and the acid–base balance. There are about one million nephrons per kidney,
- each kidneys of which is made up of five main functional segment



- The *glomeruli* ,in the cortex s capillary network of blood vessels derived from the afferent, and draining into the efferent, arterioles.
- Small molecules and water are passively filtered during the passage of blood through these capillaries,
- the **ultra filtrate** passing through the vessel walls and the glomerular membranes into the glomerular spaces (Bowman's capsules).
- ***proximal convoluted tubules***, also in the cortex, receive filtrate from the glomerular spaces.
- Convolution increases the tubular length and therefore contact between the luminal fluid and the proximal tubular cells.

- The *loops of Henle* extend down into the renal medulla and ascend again after forming the loop.
- The *distal convoluted tubules*, situated in the cortex, are important for fine adjustment of luminal fluid.
- They lie near the afferent arterioles, with the **juxtaglomerular** apparatus between them.
- **The enzyme renin is produced by the latter and its release is controlled by local blood flow**
- The *collecting ducts* start as the distal tubules lead down into the medulla and end by opening into the renal pelvis. ‘

- **Normal function of the kidneys depends on the following:**

- an adequate blood supply, which under normal circumstances is about 20 % of the cardiac output
- normal secretion and feedback control of hormones acting on the kidney,
- the integrity of the glomeruli and the tubular cells.

In addition to the excretory function and acid– base control,
the kidneys have important endocrine functions, including:

- production of 1,25-dihydroxy vitamin D, the active metabolite of vitamin D, which is produced following hepatic hydroxylation of 25-hydroxyvitamin by the renal enzyme 1-hydroxylase,
- production of erythropoietin, which stimulates erythropoiesis.

RENAL GLOMERULAR FUNCTION

About 200 L of plasma ultra filtrate usually enter the tubular lumina daily, mainly by glomerular filtration into glomerular capsules but also through the spaces between cells lining the tubules (tight junctions).

Production of ultrafiltrate depends on the blood flow through normal glomeruli and on the difference between the hydrostatic pressure gradient and the plasma effective colloid osmotic (oncotic) pressure gradient across the membranes and tight junctions.

The colloid osmotic effect is weak relative to the hydrostatic gradient but does facilitate some reabsorption of fluid from the proximal renal tubules

The filtrate contains diffusible constituents at almost the same concentrations as in plasma. Proteins (mainly low-molecular-weight

proteins) and protein bound substances are filtered in only small amounts by normal glomeruli and most are reabsorbed. The huge volume of filtrate allows adequate elimination of waste products such as urea; death from water and electrolyte depletion would occur within a few hours were the bulk of this water containing essential solutes not reclaimed.

RENAL TUBULAR FUNCTION

From the 200 L of plasma filtered daily, only about 2 L of urine are formed. The composition of urine differs markedly from that of plasma, and therefore of the filtrate. The tubular cells use adenosine triphosphate dependent active transport, sometimes selectively, against physicochemical gradients. Transport of charged ions tends to produce an electrochemical gradient that inhibits further transport. This is minimized by two processes. *Transport*

This occurs mainly in the proximal tubules Active transport of one ion leads to passive movement of an ion of the opposite charge in the same direction, along the electrochemical gradient.

The movement of sodium (Na^+) depends on the availability of diffusible negatively charged ions, such as chloride (Cl^-). The process is 'isosmotic' because the active transport of solute causes equivalent movement of water reabsorption in the same direction. Isosmotic transport also occurs to a lesser extent in the distal part of the nephron.

Ion exchange in the distal parts of the nephrons and is important for fine adjustment after bulk reabsorption has taken place.

Ions of the same charge, usually cations, are exchanged and neither electrochemical nor osmotic gradients are created.

Therefore, during cation exchange there is insignificant net movement of anions or water. For example, Na^+ may be reabsorbed in exchange for potassium (K^+) or hydrogen (H^+) ions. Na^+ and H^+exchange also occurs proximally, but at that site it is more important for bicarbonate reclamation than form fine adjustment of solute reabsorption. In the cells lining the renal tubules, the intestine and many secretory organs, the pumps are located on the membrane on one side of the cell only and therefore solute flows in one direction. Other substances, such as phosphate and urate, are secreted into, as well as reabsorbed from, the

tubular lumen. The tubular cells do not deal actively with waste products such as urea and creatinine.

Reclamation of solute from the proximal Tubule Almost all the potassium is actively reabsorbed from the proximal tubules, >70 % sodium, free ionized calcium and magnesium. Some free ionized calcium is reabsorbed at more distal sites, possibly from the loops of Henle.

This reabsorption may be stimulated by parathyroid hormone (PTH) and inhibited by loop diuretics such as furosemide.الكلام على الكالسيوم

Only about 2 % of filtered calcium appears in the urine. Specific active transport mechanisms result in the almost complete reabsorption of glucose, urate and amino acids. Some urate is secreted into the lumina, mainly in the proximal tubules, but most of this is reabsorbed.

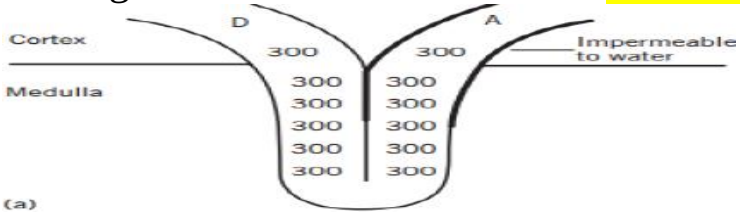
Phosphate reabsorption is incomplete; phosphate in tubular fluid is important for buffering hydrogen ions. Inhibition of phosphate reabsorption by PTH occurs in both the proximal and the distal convoluted tubules and accounts for the hypophosphataemia of PTH excess. Thus almost all the reusable nutrients and the bulk of electrolytes are reclaimed from the proximal tubules, with fine homeostatic adjustment taking place more distally.

WATER REABSORPTION: URINARYCONCENTRATION AND DILUTION

Water is always reabsorbed passively along an osmotic gradient. However, active solute transport is necessary to produce this gradient.

Two main processes are involved in water reabsorption:

- Isosmotic reabsorption of water from the proximal tubules. The nephrons reabsorb 99 % of the filtered water, about 70–80% (140–160 L/day) of which is returned to the body from the proximal tubules. Active solute reabsorption from the filtrate is accompanied by passive reabsorption of an osmotically equivalent amount of water. Therefore, fluid entering the Lumina of the loops of Henle, although much reduced in volume, is still almost isosmotic.



- Dissociation of water reabsorption from that of solute in the loops of Henle, distal tubules and collecting ducts. Normally between 40 and 60 L of water enter the loops of Henle daily. This volume is reduced to about 2 L as varying amounts of water are reabsorbed, helping to correct for changes in extracellular osmolality. At extremes of water intake, urinary osmolality can vary from about 40 to 1400 mmol/kg. The proximal tubules cannot dissociate water and solute reabsorption, and the adjustment must occur between the end of the proximal tubule and the end of the collecting duct.

Two mechanisms are involved:

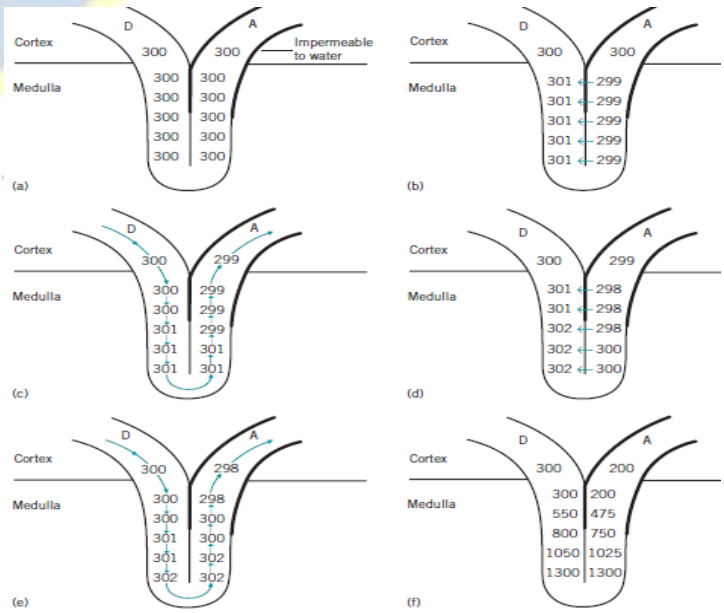
_ *Countercurrent multiplication* is an active process occurring in the loops of Henle, whereby a high osmolality is created in the renal medulla and urinary osmolality is reduced. This can occur in the absence of anti diuretic hormone (ADH), also called arginine vasopressin or vasopressin, and dilute hypo-osmolal urine is produced.

_ *Countercurrent exchange* is a passive process, occurring only in the presence of ADH. Water without solute is reabsorbed from the collecting ducts into the ascending vasa recta along the osmotic gradient created by countercurrent multiplication and by the high osmolality in the medulla, producing concentrated urine.

Countercurrent multiplication

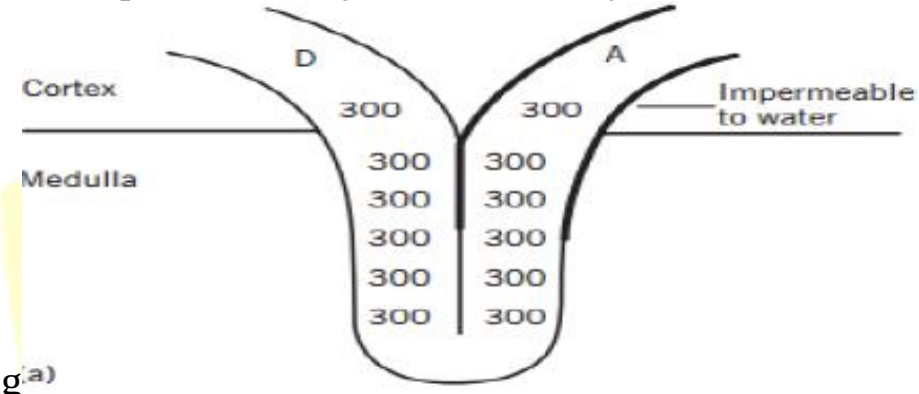
This occurs in the loops of Henle. It depends on the close apposition of the descending and ascending limbs of the loops to the vasa recta. Henle, pass deep into the medulla.

The descending limbs are permeable to water but the thick ascending limbs are impermeable to water and solute. Chloride is actively pumped from the thick ascending to the descending limbs as fluid flows through the lumina of the loops; positively charged sodium ions follow along the electrochemical gradient. Thus, the osmolality progressively



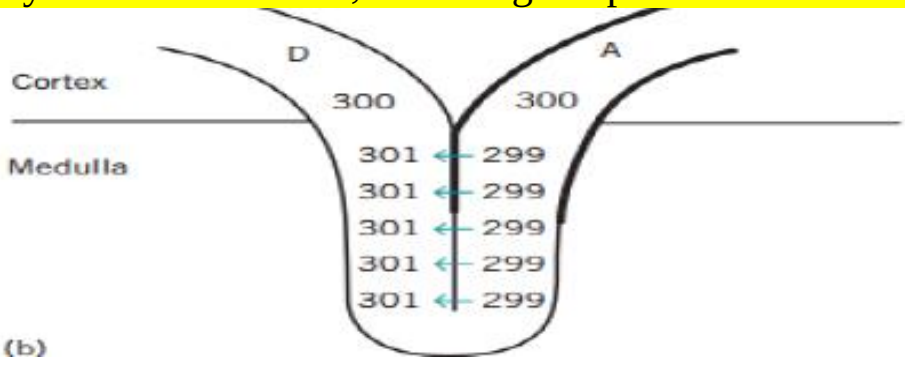
increases in the descending limbs and renal medullary interstitium; it decreases in the ascending limbs, but, as these are impermeable to water, this change is not transmitted to the interstitium.

1. The almost isosmolal fluid enters the descending limb shaving the same osmolality as the plasma, just under300 mmol/kg. If the fluid in the loops was stationary and no pumping had taken place, the osmolality through out the loops and the adjacent medullary tissue would be about

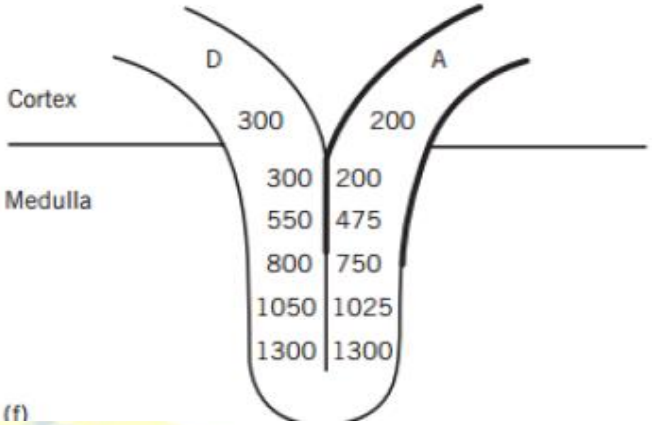


300 mmol/kg .Suppose the fluid column remained stationary and1 mmol of solute per kilogram were pumped from the ascending into the descending limb, the result. If this pumping continued and there were no flow, the fluid in the descending limb would become hyperosmolal and that in the ascending limb correspondingly hypo-osmolal .Suppose that the fluid flowed so that each figure 'moved two places' (Fig. 3.3c). As this happened, more solute would be pumped from the ascending to the descending limbs (Fig. 3.3d). If the fluid again flowed 'two places 'If these steps occurred simultaneously and continuously, the consequences would be as follows:

2. *Increasing osmolality in the tips of the loops of Henle* because the walls of most of the loops are permeable to water and solute, osmotic equilibrium would be reached with the surrounding tissues in the deeper layers of the medulla, including the plasma within the vasa recta.



3. *Hypo-osmolal fluid leaving the ascending limbs*



In the absence of ADH, the walls of the collecting ducts are impermeable to water, and therefore no further change in osmolality occurs, and hypo-osmolal urine would be passed.

Countercurrent exchange is essential, together with multiplication, for regulating the osmolal concentration of urine. It can only occur in the presence of ADH and depends on the 'random' apposition of the collecting ducts and the ascending vasa recta.

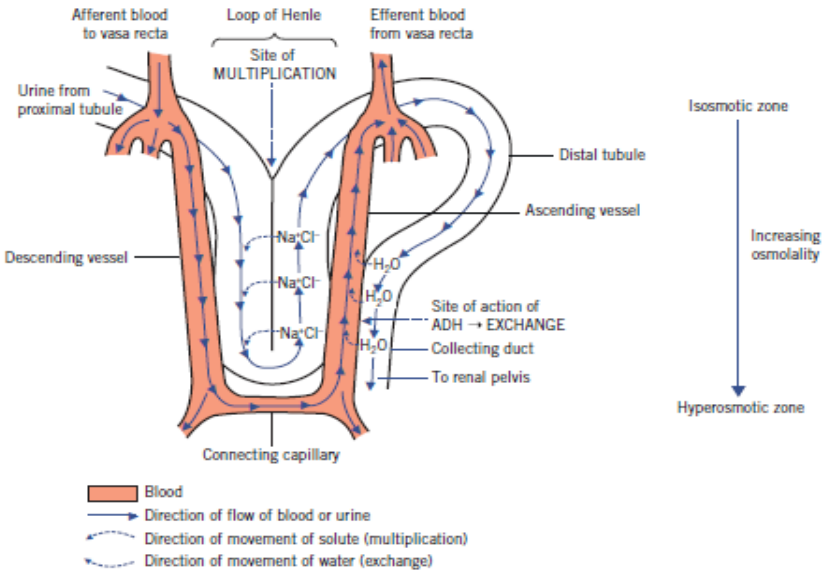
Anti diuretic hormone increases the permeability of the cell membranes (via the aquaporin's) lining the distal parts of the collecting ducts to water, which then moves passively along the osmotic gradient created by multiplication. Consequently luminal fluid is concentrated as the collecting ducts pass into the increasingly hyperosmolal medulla.

The increasing concentration of the fluid would reduce the osmotic gradient as it passes down the ducts if it did not meet even more concentrated plasma flowing in the opposite (countercurrent) direction.

The gradient is thus maintained, and water continues to be reabsorbed until the fluid reaches the deepest layers, where the osmolality is about four or five times that of plasma (Fig. 3.3f). The low capillary hydrostatic pressure at this site and the osmotic effect of plasma proteins ensure that much of the reabsorbed water within the interstitium enters the vascular lumina.

The diluted blood is carried towards the cortex and ultimately enters the general circulation and helps to dilute the extracellular fluid.

The osmotic action of urea in the medullary interstitium may potentiate the countercurrent multiplication. As water is reabsorbed from the collecting ducts under the influence of ADH, the luminal urea concentration increases. Because the distal collecting ducts are permeable to urea, it enters the



Deeper layers of the medullary interstitium, increasing the osmolality and drawing water from the lower parts of the descending limbs of the loops. The amount of urea reabsorbed depends on:

- the amount filtered,
- The rate of flow of tubular fluid: as much as 50 % of filtered urea may be reabsorbed when flow is significantly reduced.

In summary, both concentration and dilution of urine depend on active processes, which may be impaired if tubules are damaged.

Renal homeostatic control of water excretion

Water restriction

by increasing the plasma osmolality, water restriction increases ADH secretion and allows countercurrent exchange with enhanced water reabsorption. Reduced circulatory volume results in a sluggish blood flow in the vasa recta and increased urea reabsorption, allowing a build-up of the medullary hyperosmolality produced by multiplication. This potentiates water reabsorption in the presence of ADH. The reduced capillary hydrostatic pressure and increased colloid osmotic pressure, due to the haemoconcentration following non-protein fluid loss, ensure that much of the reabsorbed water enters the vascular compartment.

Water load

A high water intake dilutes the extracellular fluid, and the consequent fall in plasma osmolality reduces ADH secretion. The walls of the collecting ducts therefore remain impermeable to water and the countercurrent

multiplication produces a dilute urine and a high osmolality within the medulla and medullary vessels.

Blood from the latter flows into the general circulation, so helping to correct the fall in systemic osmolality. Increasing the circulating volume increases renal blood flow; the rapid flow in the vasa recta 'washes out' medullary hyperosmolality, returning some of the solute, without extra water, to the circulation.

Thus, not only is more water than usual lost in the urine, more solute is 'reclaimed'. Because medullary hyper osmolality, and therefore the ability to concentrate the urine maximally, is dependent on medullary blood flow, under normal circumstances urinary osmolality will be fully restored only several days after a prolonged water load has stopped.

Osmotic diuresis

An excess of filtered solute in the proximal tubular lumina impairs the bulk water reabsorption from this site by its osmotic effect. Unabsorbed solute concentration rises progressively as water is reabsorbed with other solute during passage through the proximal tubules, and this opposes further water reabsorption.

Thus a larger volume than usual reaches the loops of Henle. Moreover, fluid leaving the proximal tubules, although still isosmotic with plasma, has a lower sodium concentration than plasma. The relative lack of the major cation (sodium) to accompany the anion chloride along the electrochemical gradient inhibits the pump in the loops. The resulting impairment of build-up of medullary osmolality inhibits distal water reabsorption, under the influence of ADH from the collecting ducts, resulting in a diuresis.

Normally most filtered water leaves the proximal tubular lumina with reabsorbed solute. For example, glucose (with an active transport system) and urea (which diffuses back passively) are sometimes filtered at high enough concentration to exceed the proximal tubular reabsorptive capacity. They can then act as osmotic diuretics and cause water depletion. This is important, for example, in diabetes mellitus or in uraemia.

The most effective osmotic diuretics are substances that cannot cross cell membranes to any significant degree; therefore, they must be infused, as

they cannot be absorbed from the gut. One example is mannitol, a sugar alcohol, which is sometimes used therapeutically as a diuretic.

Homeostatic solute adjustment in the distal tubule and collecting duct

Sodium reabsorption in exchange for hydrogen ions occurs throughout the nephrons. In the proximal tubules the main effect of this exchange is on reclamation of filtered bicarbonate. In the distal tubules and collecting ducts, the exchange process is usually associated with net generation of bicarbonate to replace that lost in extracellular buffering. Potassium and hydrogen ions compete for secretion in exchange for sodium ions.

BIOCHEMISTRY OF RENAL DISORDERS

Pathophysiology

dependent on a common blood supply. Renal dysfunction of any kind affects all parts of the nephrons to some extent, although sometimes either glomerular or tubular dysfunction is predominant. The net effect of renal disease on plasma and urine depends on the proportion of glomeruli to tubules affected and on the number of nephrons involved.

To understand the consequences of renal disease it may be useful to consider the *hypothetical* individual nephrons, first with a low glomerular filtration rate (GFR) and normal tubular function, and then with tubular damage but a normal GFR. It should be emphasized that these are hypothetical examples, as in clinical reality a combination of varying degree may exist.

Uraemia is the term used to describe a raised plasma urea concentration and is almost always accompanied by an elevated creatinine concentration: in North America this is usually referred to as (a raised nitrogen concentration). azotaemia

Reduced glomerular filtration rate with normal tubular function

The total amounts of urea and creatinine excreted are affected by the GFR. If the rate of filtration fails to balance that of production, plasma concentrations will rise.

Phosphate and urate are released during cell breakdown. Plasma concentrations rise because less than normal is filtered. Most of the reduced amount reaching the proximal tubule can be reabsorbed, and the capacity for secretion is impaired if the filtered volume is too low to

accept the ions; these factors further contribute to high plasma concentrations.

A large proportion of the reduced amount of filtered sodium is reabsorbed by isosmotic mechanisms; less than usual is then available for exchange with hydrogen and potassium ions distally. This has two main outcomes:

- reduced hydrogen ion secretion throughout the nephron: bicarbonate can be reclaimed only if hydrogen ions are secreted; plasma bicarbonate concentrations will fall,
- Reduced potassium secretion in the distal tubule, with potassium retention (potassium can still be reabsorbed proximally).

If there is a low GFR accompanied by a low renal blood flow:

- Systemic aldosterone secretion will be maximal: in such cases, any sodium reaching the distal tubule will be almost completely reabsorbed in exchange for H+ and K+, and the urinary sodium concentration will be low.
- ADH secretion will be increased: ADH acting on the collecting ducts allows water to be reabsorbed in excess of solute, further reducing urinary volume and increasing urinary osmolality well above that of plasma and reducing plasma sodium concentration.

This high urinary osmolality is mainly due to substances not actively dealt with by the tubules. For example, the urinary urea concentration will be well above that of plasma. This distal response will occur only in the presence of ADH; in its absence, normal nephrons will form a dilute urine.

If the capacity of the proximal tubular cells to reabsorb solute, and therefore water, is normal, a larger proportion than usual of the reduced filtered volume will be reclaimed by isosmotic processes, thus further reducing urinary volume.

In summary will be as follows.

Plasma

- High urea (uraemia) and creatinine concentrations.
- Low bicarbonate concentration, with low pH (acidosis).
- Hyperkalaemia.
- Hyperuricaemia and hyperphosphataemia.

Urine

- Reduced volume (oliguria).
- Low (appropriate) sodium concentration – only if renal blood flow is low, stimulating aldosterone secretion.
- High (appropriate) urea concentration and therefore a high osmolality – only if ADH secretion is stimulated.

Reduced tubular function with normal glomerular filtration rate Damage to tubular cells impairs adjustment of the composition and volume of the urine. Impaired solute reabsorption from proximal tubules reduces isosmotic water reabsorption .Counter current multiplication may also be affected, and therefore the ability of the collecting ducts to respond to ADH is reduced. A large volume of inappropriately dilute urine is produced. The tubules cannot secrete hydrogen ions and therefore cannot reabsorb bicarbonate normally or acidify the urine. The response to aldosterone and therefore the exchange mechanisms involving reabsorption of sodium are impaired; the urine contains an inappropriately high concentration of sodium for the renal blood flow. Potassium reabsorption from the proximal tubule is impaired and plasma potassium concentrations may be low. Reabsorption of glucose, phosphate, magnesium, urate and amino acids is impaired. Plasma phosphate, magnesium and urate concentrations may be low. Thus, the findings in venous plasma and urine from the affected nephrons will be as follows.

Plasma

- Normal urea and creatinine concentrations (normal glomerular function).
- Due to proximal or distal tubular failure:
- low bicarbonate concentration and low pH,
- Hypokalaemia.
- Due to proximal tubular failure:
- Hypophosphatemia, hypomagnesaemia and hypouricaemia.

Urine

- Due to proximal and/or distal tubular failure:
- increased volume,
- PH inappropriately high compared with that in plasma.

- Due to proximal tubular failure:
- generalized amino aciduria,
- phosphaturia,
- Glycosuria.
- Due to distal tubular failure:
- even if renal blood flow is low, an inappropriately high sodium concentration (inability to respond to aldosterone),
- Even if ADH secretion is stimulated, an inappropriately low urea concentration and therefore osmolality (inability of the collecting ducts to respond to ADH). There may also be tubular proteinuria, which usually refers to low-molecular-weight proteins that are normally produced in the body, filtered across the glomerular membrane and reabsorbed in the proximal tubule, but appear in the urine as a result of proximal tubular damage, for example a1-microglobulin and retinol binding protein. However, tubular proteinuria also occurs when proximal tubular enzymes and proteins, such as *N*-acetyl-b-D-glucosaminidase (NAG), are released into the urine due to tubular cell injury

Clinical and biochemical features of renal Disease the biochemical findings and urine output in renal disease depend on the relative contributions of glomerular and tubular dysfunction. When the GFR falls, substances that are little affected by tubular action (such as urea and creatinine) are retained. Although their plasma concentrations start rising above the baseline for that individual soon after the GFR falls, they seldom rise above the reference range for the population until the GFR is below about 60 % of normal, although in individual patients they do rise above baseline.

Plasma concentrations of urea and creatinine depend largely on glomerular function By contrast; urinary concentrations depend almost entirely on tubular function.

However little is filtered at the glomeruli, the concentrations of substances in the initial filtrate are those of a plasma ultra filtrate. Any difference between these concentrations and those in the urine is due to tubular activity.

The more the tubular function is impaired, the nearer the plasma concentrations will be to those of urine. Urinary concentrations *inappropriate to the state of hydration* suggest tubular damage, whatever the degree of glomerular dysfunction. The plasma sodium concentration is not primarily affected by renal disease. The urinary volume depends on the balance between the volume filtered and the proportion reabsorbed by the tubules. As 99 % of filtered water is normally reabsorbed, a very small impairment of reabsorption causes a large increase in urine volume. Consequently, if tubular dysfunction predominates, impairment of water reabsorption causes polyuria, even though glomerular filtration is reduced. The degree of potassium, phosphate and urate retention depends on the balance between the degree of glomerular retention and the loss as a result of a reduced

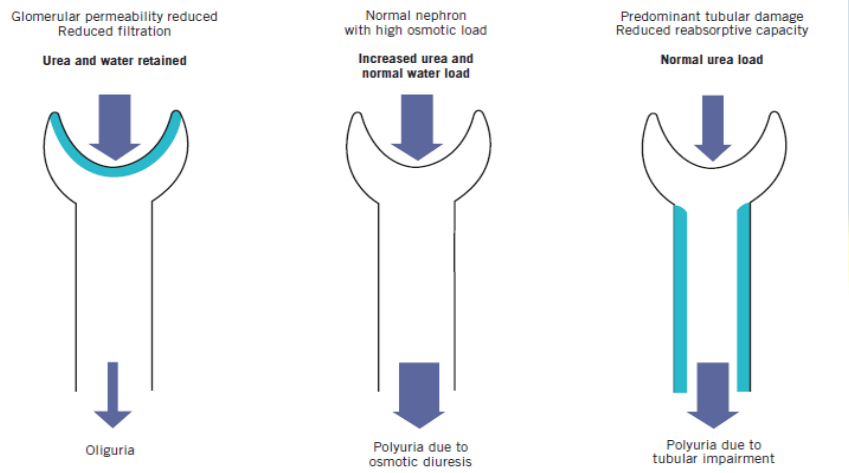


Figure 3.5 The effects of glomerular and tubular dysfunction on urinary output and on plasma concentrations of retained 'waste' products of metabolism, the volume depending on the proportion of nephrons involved.

proximal tubular reabsorptive capacity. If glomerular dysfunction predominates, so little is filtered that plasma concentrations rise, despite the failure of reabsorption.

Conversely, if tubular dysfunction predominates, glomerular retention is more than balanced by impaired reabsorption of filtered potassium, urate and phosphate, and therefore plasma concentrations may be normal or even low. A low plasma bicarbonate concentration is found in association with metabolic acidosis, which may worsen the hyperkalaemia.

Acute kidney injury this was previously known as acute renal failure. In adults, oliguria is defined as a urine output of less than 400 mL/day, or

less than 15 mL/h; it usually indicates a low GFR and a rapid decline in renal function over hours to weeks, with retention of creatinine and nitrogenous waste products.

Acute oliguria with reduced GFR (pre-renal)

This is caused by factors that reduce the hydrostatic pressure gradient between the renal capillaries and the tubular lumen. A low intracapillary pressure is the most common cause. It is known as *renal circulatory insufficiency* ('pre-renal uraemia') and may be due to:

- intravascular depletion of whole blood (haemorrhage) or plasma volume (usually due to gastrointestinal loss), or reduced intake,
- Reduced pressure as a result of the vascular dilatation caused by 'shock', causes of which include myocardial infarction, cardiac failure and intravascular haemolysis, including that due to mismatched blood transfusion. The patient is usually hypotensive and clinically volume depleted. If renal blood flow is restored within a few hours, the condition is reversible, but, the longer it persists, the greater the danger of intrinsic renal damage. As most glomeruli are involved and tubular function is relatively normal, the biochemical findings in plasma and urine are those described earlier. Uraemia due to renal dysfunction may be aggravated if there is increased protein breakdown as a result of tissue damage, a large haematoma or the presence of blood in the gastrointestinal lumen. Intravenous amino acid infusion may have the same effect because the urea is derived, by hepatic metabolism, from the amino groups of amino acids. Increased tissue breakdown may also aggravate hyperkalaemia, hyperuricaemia and hyperphosphataemia.

Acute oliguria due to intrinsic renal damage

This may be due to:

- prolonged renal circulatory insufficiency,
- acute glomeruli nephritis, usually in children – the history of a sore throat and the finding of red cells in the urine usually make the diagnosis obvious,
- septicaemia, which should be considered when the cause of oliguria is obscure,
- ingestion of a variety of poisons or drugs,
- myoglobulinuria,

- Bence Jones proteinuria.

One problem in the differential diagnosis of acute oliguria is distinguishing between renal circulatory insufficiency and intrinsic renal damage that may have followed it. Acute oliguric renal dysfunction often follows a period of reduced GFR and renal circulatory insufficiency.

The oliguria is due to reduced cortical blood flow with glomerular damage, aggravated by back-pressure on the glomeruli due to obstruction to tubular flow by edema. At this stage, the concentrations of many constituents in plasma, such as urea and creatinine, are raised with hyperkalaemia; tubular damage results in an inappropriately dilute urine for the degree of hypovolaemia. Fluid must be given with caution, and only until volume depletion has been corrected; there is a danger of overloading the circulation.

During recovery, oliguria is followed by polyuria .When cortical blood flow increases, and as tubular edema resolves, glomerular function recovers before that of the tubules. The biochemical findings gradually progress to those of tubular dysfunction until they approximate those for 'pure' tubular lesions. Urinary output is further increased by the osmotic diuretic effect of the high load of urea. The polyuria may cause water and electrolyte depletion. The initial hyperkalaemia may be followed by hypokalaemia. Mild acidosis (common to both glomerular and tubular disorders) persists until late. Recovery of the tubules may restore full renal function.

Acute oliguria due to renal outflow obstruction (postrenal)

Oliguria or anuria (absence of urine) may occur in post-renal failure. The cause is usually, but not always, clinically obvious and may be due to the following:

- *Intrarenal obstruction*, with blockage of the tubular lumina by haemoglobin, myoglobin and, very rarely, urate or calcium. Obstruction caused by casts and edema of tubular cells is usually the result of true renal damage.
- *Extra renal obstruction*, due to calculi, neoplasms, for example prostate or cervix, urethral strictures or prostatic hypertrophy, any of which may cause sudden obstruction. The finding of a palpable bladder indicates

urethral obstruction, and in males is most likely to be due to prostatic hypertrophy, although there are other, rarer, causes. Early correction of outflow obstruction may rapidly increase the urine output. The longer it remain suntreated, the greater the danger of ischaemic or pressure damage to renal tissue. Imaging studies such as renal tract ultrasound may be useful to confirm post renal obstruction (Box 3.1).

Investigation of acute kidney injury _ a careful clinical history, especially of taking nephrotoxic drugs and examination may give clues to the cause of acute kidney injury (AKI). It is essential to exclude reversible causes of pre-renal failure, including hypovolaemia or hypotension, and also post-renal urinary tract obstruction (renal tract imaging may be useful, such as abdominal radiograph if calculi are suspected, and renal tract ultrasound);

- Monitor urine output, plasma urea and creatinine and electrolytes, as well as acid–base status.
- Hyperkalaemia, hyper magnesaemia, hyperphosphataemia, hyperuricaemia and metabolic acidosis may occur in the oliguric phase of AKI.
- Urine microscopy may show granular casts supportive of the diagnosis of acute tubular necrosis.
- The urinary to plasma urea ratio can be useful, and when more than 10:1 is suggestive of pre-renal problems. The urinary to plasma creatinine or osmolality ratio may also be useful
- The fractional excretion of sodium (FENa%) is also useful diagnostically and can be

Box 3.1 Some causes of acute kidney injury (AKI)

Pre-renal
Hypotension
Hypovolaemia
Decreased cardiac output
Renal artery stenosis + angiotensin-converting enzyme inhibitor
Hepatorenal syndrome

Renal or intrinsic renal disease
Acute tubular necrosis, e.g. hypotension, toxins, contrast media, myoglobinuria, sepsis, drugs, sustained pre-renal oliguria
Vasculitis
Glomerulonephritis
Drugs that are nephrotoxic, e.g non-steroidal anti-inflammatory drugs
Sepsis
Thrombotic microangiopathy or thromboembolism
Atheroembolism
Bence Jones proteinuria
Interstitial nephritis
Infiltration, e.g. lymphoma
Severe hypercalcaemia
Severe hyperuricaemia

Post-renal
Calculi
Retroperitoneal fibrosis
Prostate hypertrophy/malignancy
Carcinoma of cervix or bladder

measured using a simultaneous blood sample and spot urine
Acute tubular necrosis, e.g. hypotension, toxins,

chronic kidney disease

Chronic renal dysfunction [defined as being reduced eGFR (estimated GFR), proteinuria, haematuria and/or renal structural abnormalities of more than 90 days' duration] is usually the end result of conditions such as diabetes mellitus, hypertension, primary glomerulonephritis, autoimmune disease, obstructive uropathy, polycystic disease, renal artery stenosis, infections and tubular
Dysfunction and the use of nephrotoxic drugs
chronic renal dysfunction may pass through two main phases:

- an initially polyuric phase,
- Subsequent oliguria or anuria, sometimes needing dialysis or renal transplantation.

Polyuric phase

At first, glomerular function may be adequate to maintain plasma urea and creatinine concentrations within the reference range. As more glomeruli are involved, the rate of urea excretion falls and the plasma concentration rises. This causes an osmotic diuresis in functioning nephrons; in other nephrons the tubules may be damaged out of proportion to the glomeruli.

Oliguric phase

If nephron destruction continues, the findings become more like those of pure glomerular dysfunction.
Glomerular filtration decreases significantly and urineoutput falls; oliguria precipitates a steep rise in plasma urea, creatinine and potassium concentrations; and the metabolic acidosis becomes more severe. However, haematuria may originate from either the kidney or the urinary tract, and may therefore indicate the presence of other conditions, such as urinary tract infections, renal calculi or tumours

Other abnormal findings in chronic kidney disease

Apart from uraemia, hyperkalaemia and metabolic acidosis, other abnormalities that may occur in CKD include the following:

- Plasma phosphate concentrations rise and plasma total calcium concentrations fall

- Plasma urate concentrations rise in parallel with plasma urea.
- Hypermagnesaemia
- Normochromic, normocytic anaemia due to erythropoietin deficiency is common and, because haemopoiesis is impaired
- commonest causes of death in patients with CKD is cardiovascular disease,
- Abnormal endocrine function, such as hyperprolactinaemia, insulin resistance, low plasma
- Some of the features of CKD may be explained by the presence of 'middle molecules'

The presence of proteinuria best predictor of disease progression.

SYNDROMES REFLECTING PREDOMINANT TUBULAR DAMAGE –RENAL TUBULAR ACIDOSIS:

- There is a group of conditions that primarily affect tubular function more than the function of the glomeruli. However, scarring involving whole nephrons may eventually cause chronic renal dysfunction.
- Impaired function may involve a single transport system, particularly disorders associated with amino acid or phosphate transport, or may affect multiple transport systems. Conditions associated with multiple transport defects may cause renal tubular acidoses – renal tubular disorders associated with a systemic metabolic acidosis because of impaired reclamation of bicarbonate or excretion of H+
- Disorders affecting the urine-concentrating mechanism and causing nephrogenic diabetes insipidus but which rarely in themselves cause a metabolic acidosis are discussed elsewhere

NEPHROTIC SYNDROME:

- The nephrotic syndrome is caused by increased glomerular basement membrane permeability, resulting in protein loss, usually more than 3 g a day (or a urine protein to creatinine ratio of > 300 mg/mmol), with consequent hypoproteinaemia, hypoalbuminaemia and peripheral edema.

• All but the highest molecular weight plasma proteins can pass through the glomerular basement membrane. The main effects are on plasma

proteins and are associated with hyperlipidaemia and hyper fibrinoginaemia. Uraemia occurs only in late stages of the disorder, when many glomeruli have ceased to function.

NEPHRITIC SYNDROME:

• This comprises reduced eGFR, oedema, hypertension and proteinuria with significant haematuria. It is usually associated with systemic disease such as post infectious glomerulonephritis, e.g. post-streptococcal or immunoglobulin A (IgA) nephropathy, ANC Aassociated vasculitis, e.g. Wegener's granulomatosis or microscopic polyarteritis, or antiglomerular basement membrane disease (Goodpasture's disease).

DIAGNOSIS OF RENAL DYSFUNCTION:

Glomerular function tests: As glomerular function deteriorates, substances that are normally cleared by the kidneys, such as urea and creatinine, accumulate in plasma.

Measurement of plasma concentrations of urea and creatinine:

• Urea is derived in the liver from amino acids and therefore from protein, whether originating from the diet or from tissues. The normal kidney can excrete large amounts of urea.

• If the rate of production exceeds the rate of clearance, plasma concentrations rise.

• The rate of production is accelerated by:

● a high-protein diet, ● absorption of amino acids and peptides from digested blood after haemorrhage into the gastrointestinal lumen or soft tissues, ● increased catabolism due to starvation, tissue damage, sepsis or steroid treatment.

In catabolic states, glomerular function is often impaired due to circulatory factors and this contributes more to the uraemia than does increased production. Conversely, the plasma urea concentration may be lower than 1.0 mmol/L, the causes of which include the following: those due to increased GFR or haemodilution (common): – pregnancy (the commonest cause in young women), – overenthusiastic intravenous

infusion (the commonest cause in hospital patients), – 'inappropriate' ADH secretion (syndrome of inappropriate ADH secretion, SIADH). ● those due to decreased synthesis
– use of amino acids for protein anabolism during growth, especially in children, – low protein intake, – very severe liver disease (low amino acid deamination), – inborn errors of the urea cycle are rare and usually only occur in infants.
• Creatinine is largely derived from endogenous sources by muscle creatine breakdown. Plasma creatinine usually correlates with muscle mass, with 95 per cent of creatine occurring in skeletal muscle.
• The plasma creatinine concentration varies more than that of urea during the day owing to creatine intake in meals. However, sustained high-protein diets and catabolic states probably affect the plasma concentration of creatinine less than that of urea. Creatinine concentration is used to assess renal function; however, its assay may be less precise than that of urea, and can be prone to analytical interference by substances such as bilirubin, ketone bodies and certain drugs.

- If the plasma concentration of either urea or creatinine is significantly raised, and especially if it is rising, impaired glomerular function is likely.
- Serial changes may be used to monitor changes in the GFR and changes greater than 10–15 per cent are likely to be clinically significant.
- With a reduced GFR, plasma urea concentrations tend to rise faster than those of creatinine and tend to be disproportionately higher with respect to the upper reference limit.

The rate at which urea is reabsorbed from the collecting ducts is dependent on the amount filtered by the glomerulus and by the rate of luminal fluid flow

Clearance as an assessment of glomerular filtration:

For a substance (S) that is filtered by the glomerulus, but not reabsorbed from or secreted into the tubules, the amount filtered (GFR * plasma[S]) must equal the
1-the GFR thus measured is referred to as the *clearance* the volume of plasma
2-theoretically be completely cleared of a substance in 1 min.

True measurement substance:

1- Only substances freely filtered by glomeruli
2- not acted on by the tubules
There is no such endogenous substance, but inulin, a polysaccharide, fulfils the criteria closely. Inulin is not produced by the body; it must be given either by constant infusion in order to maintain steady plasma concentrations during the period of the test, or by a single injection followed by serial blood sampling
Radiochromium- labelled ethylenedi amine tetra acetic acid (EDTA) is another exogenous compound that some consider the 'gold standard' for calculating patient GFR, although this requires the use of nuclear medicine tests is rarely used

Creatinine increase:

1-Those with muscle breakdown may show higher plasma creatinine concentration and the converse may be seen in those with reduced muscle bulk.
2-There may be increased muscle bulk in black compared with white people.
3-Individuals taking creatine supplements for body building may show increased plasma creatinine and also plasma creatine kinase (CK)
Creatinine clearance is higher than inulin clearance because some creatinine is secreted by the tubules. Urea clearance is lower than inulin clearance as some urea is Reabsorbed into the tubules؟ وين
various factors that make the measurement of creatinine clearance inaccurate
1- All laboratory assays have an inherent imprecision. The combined imprecision of two assays is greater than that of one .
2- Inaccurate urine collection may yield misleading results. The difficulties are increased in infants and young children, and in patients who have difficulty in bladder emptying or are incontinent
3- Both creatinine and urea may be partly destroyed by bacterial action in infected or old urine. The reciprocal of the plasma creatinine concentration is called the *renal index*.

Cystatin C

Another endogenous substance that can be used as a marker of GFR is plasma cystatin C , and its use may alleviate some of the problems associated with creatinine clearance determinations.
This is a 13-kDa protein that is a member of the family of cystine proteinase inhibitors. Unlike other endogenous compounds such as creatinine, Cys C is not secreted by the renal tubules and does not return to the bloodstream after glomerular filtration. It has been suggested that plasma Cys C may approximate to *the 'ideal' endogenous marker for GFR,* as blood concentrations are independent of patient age and sex

• URINARY SODIUM AND OSMOLALITY

Urinary sodium estimation Urinary sodium estimation may be used to differentiate acute oliguria due to renal damage from that due to renal circulatory insufficiency. *Aldosterone secretion will be maximal only if renal blood flow is reduced*; in such circumstances, functioning tubules respond appropriately by selectively reabsorbing sodium by distal tubular exchange mechanisms.
A urinary sodium concentration of less than about 20 mmol/L is usually taken to indicate that tubular function is not significantly impaired.
• Acute kidney injury treatment
1- Pre-renal AKI 1- reserve fluid balance and prompt treatment of hypovolaemia. 2- Sometimes furosemide with mannitol or dopamine infusion may reestablish normal urine flow.
intrinsic damage restrict fluid and sodium intake, giving only enough fluid to replace losses and provide an adequate
low-protein energy intake to minimize aggravation of uraemia.
the cause of the intrinsic renal failure should be treated. 4- Careful attention should be given to nephrotoxic drugs in AKI.post-renal failure, prompt relief of the obstruction may reverse the situation.
A polyuric phase may occur, particularly on relief of urinary obstruction with excretion of potassium and magnesium, and this can result in hypovolaemia, hypokalaemia and hypomagnesaemia, which may need correcting.
Renal replacement therapy (RRT) such as dialysis or haemo filtration may improve fluid and electrolyte imbalances . RRT is important to prevent dangerous hyperkalaemia or if resistant pulmonary oedema is present.
• **Chronic kidney disease**
1- Careful control of fluid and electrolyte balance is important; water intake is usually only restricted if the plasma sodium concentration is not maintained. Similarly, sodium intake should be unrestricted unless contraindications such as hypertension or oedema exist.
2-Plasma potassium monitoring is essential and potassium restriction may become necessary (and avoidance of potassium-retaining medication) if there is hyperkalaemia, which may need specific therapy and can be life threatening
• Control of blood pressure, lipids and, if present, diabetes mellitus slow decline of eGFR and reduce cardiovascular risk. Angiotensin-converting enzyme inhibitors slow the decline in renal function, although patients should be monitored for hyperkalaemia.
increased caloric intake along with reduced dietary protein intake may slow the decline in GFR by reducing protein catabolism.

• **hyperphosphataemia** and the calcium phosphate Tissue precipitation of calcium to phosphate this reduced by
1- adequate fluid intake.
2-Dietary phosphate restriction is used in the early stages of chronic renal dysfunction.
3- If the plasma phosphate concentration is raised, phosphate-binding agents such as calcium acetate or carbonate may be indicated.
• When GFR is below 60 mL/min per 1.73 m2, secondary hyperparathyroidism with elevated PTH concentration occurs.
1- Giving small doses of active vitamin D, such as calcitriol or alfacalcidol, reduces the serum PTH, and improves bone histology, and leads to increased bone mineral density and helps
avoid renal osteodystrophy, Recombinant erythropoietin and iron therapy may be indicated to treat anaemia when haemoglobin is less than 11 g/dL
• Dialysis
• Haemofiltration is a form of haemodialysis in which large volumes of fluid and solute can be removed through a highly permeable membrane;
dialysis is dependent primarily on the blood pressure. Haemofiltration is mainly used for AKI whereas the following forms of dialysis are mainly for CKD
• In haemodialysis, blood is passed through an extracorporeal circulation and dialysed across an artificial membrane with a solution before being returned to the body.
• In intermittent and continuous ambulatory peritoneal dialysis, the folds of the peritoneum are used as the dialysing membrane with capillaries on one side, and an appropriate fluid of higher osmolality is infused into the peritoneal cavity on the other

RENAL CALCULI

Conditions favouring renal calculus formation
1- A high urinary concentration of one or more constituents of the glomerular filtrate, due to:
1- a low urinary volume with normal renal function, because of restricted fluid intake
2- excessive fluid loss over a long period of time this favours formation of most types of calculi.
3-a high rate of excretion of the metabolic product forming the stone
4- a high rate of excretion of the metabolic product forming the stone,

5- Urinary stagnation due to obstruction to urinary outflow or renal tract structural abnormality.
6- Lack of normal inhibitors: urine normally contains inhibitors, such as citrate, pyrophosphate and glycoproteins, which inhibit the growth of calcium phosphate and calcium oxalate crystals respectively.
• Constituents of urinary calculi Renal calculi may consist of the following : ● calcium-containing salts: – calcium oxalate, – calcium phosphate, ● urate, ● cystine, ● xanthine
• Calculi composed of calcium salts: About 80 per cent of all renal stones contain calcium.
• Increase ca in urine cause stone and the type of salt depends on urinary pH and on the availability of oxalate. Any patient presenting with calcium containing calculi should have plasma calcium and phosphate estimations performed, and, if the results are normal, they should be repeated at regular intervals to primary hyperparathyroidism.
• many subjects with calcium-containing renal calculi the plasma calcium concentration is normal
• Acidosis
• Hypercalciuria has been defined as a daily urinary calcium excretion of more than 6.2 mmol in adult females and 7.5 mmol in adult males
• Hyperoxaluria favours the formation of the very poorly soluble calcium oxalate, even if calcium excretion is normal. The source of the oxalate may be derived exogenously from the diet. Oxalate absorption is increased by fat malabsorption: Foods rich in oxalate include rhubarb, chocolate, beetroot, spinach, nuts and tea
• Primary hyperoxaluria, a rare inborn error, should be considered if renal calculi occur in childhood. There are two main types
• Type 1 is due to deficiency of alanine glyoxylate aminotransferase
• type2 is due to deficient D-glycerate dehydrogenase.
• Hyperoxaluria (urinary oxalate greater than 400 µmol/24 h) is a more important risk factor for formation of renal stones than is hypercalciuria
• Alkaline conditions favouring calcium phosphate precipitation and stone formation are particularly common in patients with chronic renal infection.
• treatment of calcium-containing calculi depends on the cause. Urinary calcium concentration should be reduced: by treating hypercalcaemia if present, if this is not possible, by reducing dietary calcium (although this alone may exacerbate hyperoxaluria) and oxalate intake, ● by maintaining a high fluid intake, unless there is glomerular failure.

Thiazide diuretics reduce urinary calcium excretion and treatment of urinary tract infection may reduce the risk of calculi formation.

• Struvite (magnesium ammonium phosphate) These stones (about 10 per cent of all renal calculi) are associated with chronic urinary tract infections by organisms such as *Proteus* species capable of splitting ammonium.

• Uric acid stones About 8 per cent of renal calculi contain uric acid; these are sometimes associated with hyperuricaemia, with or without clinical gout. In most cases, no predisposing cause can be found•

• Cystine stones: are rare. In normal subjects the concentration of cystine in urine is soluble, but in homozygous cystinuria this may be exceeded and the patient

• Miscellaneous stones Xanthine stones Xanthine stones are very uncommon and may be the result of the rare inborn error xanthinuria.

• Other stones : Other rare stones may consist of dihydroxyadenine (due to adenine phosphoribosyltransferase deficiency) or poorly calcified

Indinavir stones

These are seen in patients with human immunodeficiency virus (HIV) infection who have been treated with the protease inhibitor indinavir. The stones are composed of pure protease inhibitor

• Treatment of renal calculi

• Apart from specific treatments, patients with a tendency to form calculi are generally advised to drink more water. The aim is usually to increase the urinary volume to about 2–3 L in 24 h.

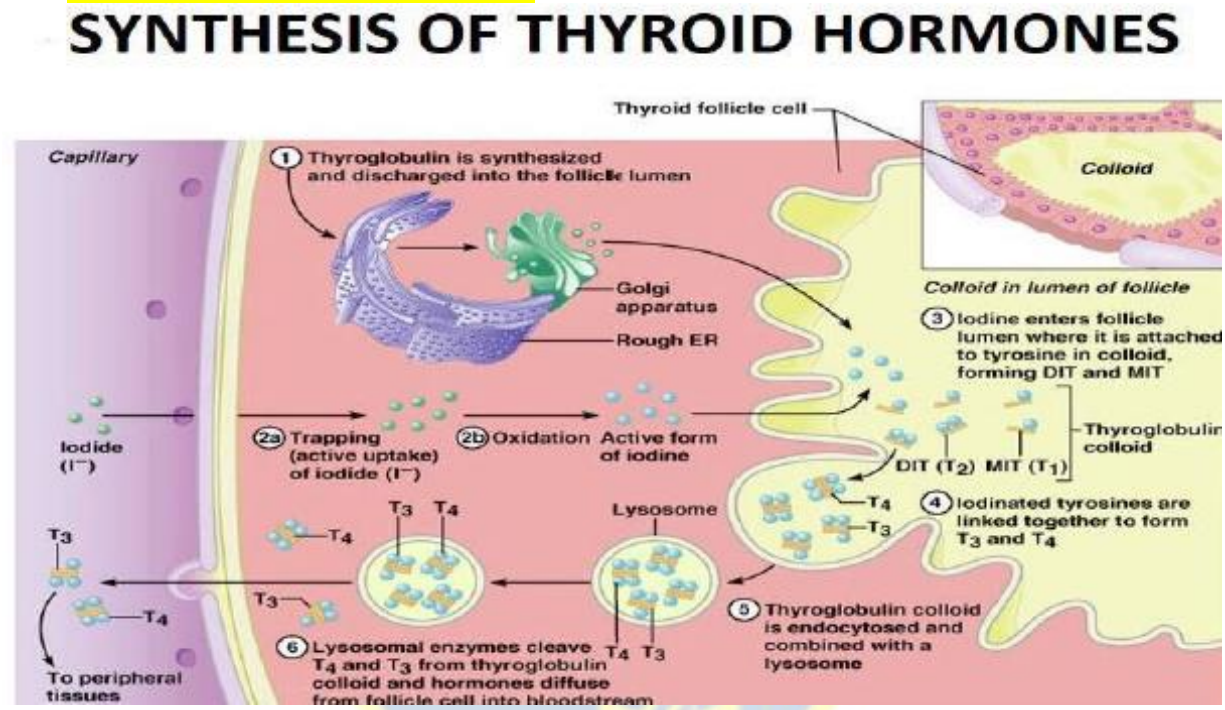
• Reducing calcium intake may not be advisable, as it may increase oxalate absorption and excretion.

• Calculi removal by fragmentation using extracorporeal shock wave lithotripsy has in some cases reduced the need for surgical intervention.

Chapter two

Thyroid function

Briefly, thyroxine (T4), tri-iodothyronine (T3) and calcitonin are secreted by the thyroid gland. Both T4 and T 3 are products of the follicular cells and influence the rate of all metabolic processes. Calcitonin is produced by the specialized C cells and influences calcium metabolism.



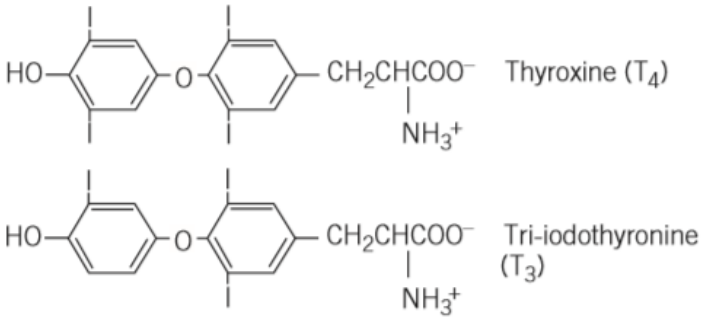
• Protein binding of thyroid hormones in plasma Most of the plasma T4 and T3 is protein bound, mainly (70 per cent) to an a-globulin, thyroxine-binding globulin (TBG), and, to a lesser extent (15 per cent), transthyretin (previously called pre-albumin), with about 10–15 per cent bound to albumin.

• In keeping with many other hormones, the free unbound fraction is the physiologically active form, which also regulates TSH secretion from the anterior pituitary.

• Peripheral conversion of thyroid hormone Some of the circulating T4 is de-iodinated by enzymes in peripheral tissues, especially in the liver and kidneys. About 80 per cent of the plasma T3 is produced by the removal of an iodine atom from the outer (b) ring; the remaining 20 per

cent is secreted by the thyroid gland. De-iodination of the inner (a) ring produces reverse T3, which is probably inactive.

• The T3 binds more avidly to thyroid receptors than T4 and is the main active form.



• The conversion of T :4 to T3 may be:

● *reduced* by many factors, of which the most important are:

– systemic illness, – prolonged fasting, – drugs such as b-blockers, for example propranolol or amiodarone (200 mg of this anti-arrhythmic drug contains about 75 mg of iodine);

● *increased* by drugs that induce hepatic enzyme activity, such as phenytoin

• The plasma T3 concentration is therefore a poor indicator of thyroid hormone secretion because it is influenced by many non-thyroidal factors and its measurement is rarely indicated, except if thyrotoxicosis is suspected.

• Action of thyroid hormones

1-Thyroid hormones affect many metabolic processes, increasing oxygen consumption. They bind to specific receptors in cell nuclei and change the expression of certain genes.

2- Thyroid hormones are essential for normal growth, mental development and sexual maturation and also increase the sensitivity of the cardiovascular and central nervous systems to catecholamines, thereby influencing cardiac output and heart rate.

• Control of thyroid-stimulating hormone secretion Thyroid-stimulating hormone stimulates the synthesis and release of thyroid hormones from the thyroid gland. Its secretion from the anterior pituitary gland is controlled by thyrotrophin-releasing hormone (TRH) and circulating concentrations of thyroid hormones.

• Effects of thyroid hormones in the control of thyroid stimulating hormone secretion Thyroid hormones reduce TSH secretion by negative

feedback. Tri-iodothyronine binds to anterior pituitary nuclear receptors.
In the anterior pituitary gland, most of the intracellular T 3 is derived from circulating fT4 Therefore this gland is more sensitive to changes in plasma T4 than to T3 concentrations.

• THYROID FUNCTION TESTS

Assessment of thyroid hormone secretion can be made by measuring plasma TSH as well as either fT4 or total T4 [sometimes also free T3 (fT3) or total T3]
• Plasma thyroid-stimulating hormone Concentrations of TSH are high in primary hypothyroidism and low in secondary or pituitary hypothyroidism.
• In hyperthyroidism, high plasma T4 and T 3 concentrations suppress TSH release from the pituitary, resulting in very low or undetectable plasma TSH concentrations.
• Plasma TSH assays are used as first-line assays for thyroid function assessment. New generation assays have high sensitivity and have a detection limit for plasma TSH of less than 0.1 mU/L.
• Plasma total thyroxine or free thyroxine assays Plasma T4 is more than 99 percent protein bound; therefore, plasma total T4 assays reflect the protein bound rather than the free hormone fraction. Total T4 reflects fT4 concentrations, unless there are abnormalities of binding proteins. ● In the *euthyroid* state, about a third of the binding sites on TBG are occupied by T4 and the remainder are unoccupied, irrespective of the concentration of the binding protein. ● In *hyperthyroidism*, both plasma total and fT4 concentrations are increased and the number of unoccupied binding sites on TBG is decreased. ● In *hypothyroidism*, the opposite of the above occurs.
• An increase in plasma TBG concentration causes an increase in both bound T 4 and unoccupied binding sites but no change in plasma fT4 concentrations.
• Such an increase may occur because of:

1- a high estrogen concentration during pregnancy or in the newborn infant, estrogen therapy, for example certain oral contraceptives or hormone replacement therapy, ● inherited TBG excess (rare). A decrease in plasma TBG concentration decreases both bound T4 concentrations and unoccupied binding sites, but does not alter the plasma fT4 concentration.

2- Such changes may occur because of : ● severe illness, but this is usually temporary, ● loss of low-molecular-weight proteins, usually in the urine, for example nephrotic syndrome, ● androgens or danazol treatment, ● inherited TBG deficiency (rare).

• These changes might be misinterpreted as being diagnostic of hyperthyroidism or hypothyroidism respectively if only plasma total T4 was assayed and it is for this reason that fT4 concentrations are now generally preferred. Some drugs, such as salicylates and danazol, bind to TBG and displace T4. The change in unoccupied binding sites is variable and TBG concentrations are unaffected. Measurement of plasma TBG concentrations may occasionally be indicated to confirm either congenital TBG excess or deficiency.

• Plasma total or free tri-iodothyronine

• Total T3 or fT3 concentrations may help in the diagnosis of hyperthyroidism but are not usually used routinely to diagnose hypothyroidism because normal plasma concentrations are very low. In hyperthyroidism, the increase in plasma T3 or fT3 concentrations is greater, and usually occurs earlier than that of T4 or fT4. Occasionally in hyperthyroidism the plasma T3 or fT 3 concentrations are elevated but not those of T4 or fT 4 (T3 toxicosis). Like T4, T3 is bound to protein. It is usually preferable to measure the plasma concentration of fT3 rather than total T3, as the latter may be altered by changes in the plasma concentrations of TBG.

• Thyrotrophin-releasing hormone test The TRH test is used to confirm the diagnosis of secondary hypothyroidism, or occasionally to diagnose early primary hypothyroidism.

• Since the development of sensitive TSH assays, it is rarely used to diagnose hyperthyroidism, although it may have a place in the differential diagnosis of thyroid resistance syndrome or TSH-secreting pituitary tumours (TSHomas) .
• Allergic reactions may occur, and therefore resuscitation facilities should be available and the test should be carried out by experienced staff.
• Procedure ● A basal blood sample is taken. ● 200 µg of TRH is injected intravenously over about a minute. ● Further blood samples are taken 20 and 60 min after the TRH injection, and TSH is measured in all samples. Note that certain drugs, such as dopamine agonists and glucocorticoids, reduce the response, and estrogens, metoclopramide and theophylline enhance it.
• İnterpretation In normal subjects, plasma TSH concentration increases at 20 min by at least 2 mU/L and exceeds the upper limit of the reference range, with a small decline at 6 min. ● An exaggerated response at 20 min and a slight fall at 60 min are suggestive of primary hypothyroidism. ● A normal or exaggerated increment but delayed response, with plasma TSH
concentrations higher at 60 min than at 2 min, suggests secondary hypothyroidism.
• If clinically indicated, pituitary and hypothalamic function should be investigated.
• Drug effects on thyroid function tests
• **DISORDERS OF THE THYROID GLAND** The most common presenting clinical features of thyroid disease are the result of:
● *hypothyroidism*, due to deficient thyroid hormone secretion,
● *hyperthyroidism*, due to excessive thyroid hormone secretion,
● *goitre*, either diffuse or due to one or more nodules within the gland – there may or may not be abnormal thyroid hormone secretion and thus the patient may be euthyroid.
• Hypothyroidism: is caused by suboptimal circulating concentrations of thyroid hormones. It becomes more prevalent with age, affecting about

6 per cent of people over 60 years, and is more common in women. The condition may develop insidiously and in its early stages may cause only vague symptoms. There is a generalized slowing down of metabolism, with lethargy, bradycardia, depression and weakness

• If the hormone deficiency is caused by a primary disorder of the thyroid gland, the patient may present

1- with weight gain

2- myopathy

3-menstrual disturbances such as menorrhagia, constipation.

4-The skin may be dry, the hair may fall out and the voice may be hoarse. 5- Subcutaneous tissues are thickened; this pseudo-edema, with a histological myxoid appearance, accounts for the term myxoedema, which is sometimes used to describe advanced hypothyroidism.

6-In severe cases, coma with profound hypothermia may develop.

• laboratory changes

• Plasma cholesterol concentration. In hypothyroidism the clearance of plasma low-density lipoprotein (LDL) cholesterol is impaired and plasma cholesterol concentrations may be moderately high.

● Plasma creatine kinase activity is often raised in hypothyroidism, due to possible myopathy

• Hyponatraemia may very rarely present in patients with profound hypothyroidism or myxedema coma. It is caused by increased antidiuretic hormone release with excessive water retention, occasionally Hypothyroidism may be associated with hyperprolactinaemia.

● Plasma sex-hormone-binding globulin (SHBG) concentration is reduced in hypothyroidism.

● A macrocytic anaemia may be observed, with raised mean corpuscular volume (MCV).

● In severe hypothyroidism a reduced estimated glomerular filtration rate may occur probably due to impaired renal perfusion

• Cause Primary

1- the most common cause of hypothyroidism worldwide is iodine deficiency.
2- In areas of adequate iodine intake, acquired hypothyroidism is mainly due to autoimmune thyroiditis or Hashimoto's thyroiditis, which is more frequently seen in women and the elderly. About 90 per cent of patients have positive thyroid antibodies, for example anti-thyroid peroxidase (antiTPO), anti-thyroglobulin (anti-Tg) or TSH receptor blocking antibodies. There may also be a goitre.
Hypothyroidism may also be associated with other autoimmune diseases such as type 1 diabetes mellitus, adrenal insufficiency and pernicious anaemia.
3- Rare causes of primary hypothyroidism are exogenous goitrogens (substances that interfere with thyroid iodine uptake and thus can result in a goitre) and dyshormonogenesis, a term that includes inherited deficiencies of any of the enzymes involved in thyroid hormone synthesis, which may present in childhood. Although the biochemical and clinical features differ, the end result is

hypothyroidism. In most cases, prolonged TSH stimulation, due to reduced negative feedback, causes goitre.
• The most common form is due to failure to incorporate iodine into tyrosine . The perchlorate discharge test may be useful to diagnose iodination and trapping defects, although it is rarely used.
• Secondary
• Secondary hypothyroidism is due to low concentrations of TSH from the anterior pituitary or to hypothalamic TRH deficiency; this is much less common than primary hypothyroidism.
• In long-standing secondary hypothyroidism, the thyroid gland may atrophy irreversibly. The essential biochemical difference between primary and secondary hypothyroidism is in the plasma TSH concentration, which is high in the former and inappropriately low in the latter

• Very rarely a ‘consumption’ hypothyroidism is seen in individuals with extensive haemangioma which contains iodothyronine deiodinase. This seleno enzyme catalyses the conversion of T4 to reverse tri-iodothyronine and the conversion of T3 to 3,3¢-diiodothyronine, both of which are biologically inactive.
• Pathophysiology As primary hypothyroidism develops, TSH secretion from the anterior pituitary gland increases as the negative feedback (associated with the falling plasma 4 or fT4 concentration) decreases. Plasma T3 or fT3 concentrations may be normal and thus not usually useful in making the diagnosis. Initially, the plasma T4 or fT4 concentration may be within the population reference range, although abnormally low for the individual. For this reason the plasma TSH concentration is the most sensitive index of early hypothyroidism. If the patient is very ill, investigations should be deferred
• Treatment of hypothyroidism: This is usually with T4, which can be titrated until the plasma TSH is within the reference range. However, this has recently been challenged, as plasma TSH concentrations may not adequately reflect tissue
hypothyroidism, and it may be better to be guided by plasma fT4 concentrations and clinical features. On rare occasions, such as in hypothyroid comas, T3 is given instead, as its action is more immediate.
• The response to T4 therapy can be checked every 2–3 months until the patient is stable, after which 6- to 12-month blood checks may be useful.
• Thyroxine should be used with caution in patients with ischaemic heart disease for fear of worsening angina pectoris, and low doses initially plus b-blockers may be indicated.
• Thyroid-stimulating hormone assays are of little value in monitoring secondary hypothyroidism; fT 4 is better.
• Thyroxine therapy may precipitate an Addisonian crisis in patients with concomitant adrenal insufficiency.
• Overtreatment with T4 can evoke atrial fibrillation and osteoporosis; in such cases, plasma TSH concentrations are often low or suppressed.

If a patient is non-compliant with treatment and only takes T4 near to the time of thyroid function testing, a high plasma TSH may be observed with high plasma fT4 concentrations.

• This is because there is insufficientT4 to normalize plasma TSH, and yet the high plasma fT4 reflects the recent taking of T4.

• Subclinical hypothyroidism Subclinical (compensated hypothyroidism) is the state in which plasma TSH concentration is raised but the total or fT 4 concentration still falls within the reference range.

• In individuals over the age of 60 years, the prevalence may be as high as 10 per cent. Some of these patients have positive thyroid antibodies, for example anti-TPO or anti-Tg, and each year about 2–5 per cent of thyroid antibody-positive patients go on to develop hypothyroidism. Some patients may be asymptomatic, whereas others have symptoms suggestive of hypothyroidism.

Drug	T_4	fT_4	T_3	fT_3	Remarks
Amiodarone	↑	Normal or ↑	Normal	Normal	Blocking T_4 to T_3 conversion
Androgens	↓	Normal	↓	Normal	Reduced TBG
Carbamazepine	↓	↓	Normal	Normal	Increased T_4 to T_3 conversion
Carbimazole	↓	↓	↓	↓	Therapeutic if thyrotoxic
Lithium	↓	↓	↓	↓	Lithium may inhibit iodination
Estrogens	↑	Normal	↑	Normal	Increased TBG
Phenytoin	↓	↓	Normal	Normal	Increased T_4 to T_3 conversion
Propranolol	Normal	Normal	↓	↓	Blocking T_4 to T_3 conversion
Propylthiouracil	↓	↓	↓	↓	Therapeutic if thyrotoxic
Salicylate	↓	Normal	↓	Normal	Reduced TBG binding
Some radiocontrast media	↑	Normal	↓	Normal or ↓	Blocking T_4 to T_3 conversion (transient effect)

• Thyroxine therapy may be indicated particularly in pregnancy, when the patient is symptomatic, or with positive thyroid antibodies and plasma TSH more than 10 mU/L. It can be associated with increased risk of cardiovascular disease.

• Thyroid hormone resistance In generalized thyroid hormone resistance, the plasma total T 4 and fT4 concentrations are elevated, with normal or slightly raised TSH concentration.
• Some patients appear euthyroid, but others may present with hypothyroid symptoms, and the defect may be inherited as an autosomal dominant trait in some patients.
• The defect is thought to be due to a defect in T4 and/or T3 receptors and may be associated with other end-organ resistance states.
• Laboratory investigation of suspected hypothyroidism 1- A careful history (including drugs) should be taken and an examination performed, checking for a goitre.
● The plasma TSH and total T4 or fT4 concentrations should be measured.
● Slightly elevated plasma TSH and normal fT4 concentrations suggest compensated hypothyroidism. Measuring circulating thyroid antibodies may be useful, that is, anti-TPO. Tests should be repeated after 3–6 months as some patients may develop full blown hypothyroidism.
● Raised plasma TSH and low fT4 concentrations suggest primary hypothyroidism. The thyroid antibodies should be measured and, if positive, other autoimmune diseases excluded.
• Low plasma TSH and low fT4 concentrations may indicate that the hypothyroidism is caused by a hypothalamic or pituitary disorder. A TRH test should be done, if indicated, and the pituitary gland assessed.
● Raised plasma TSH and raised/normal plasma fT4 concentrations in the presence of hypothyroid symptoms may indicate thyroid hormone resistance.
•hyperthyroidism (thyrotoxicosis) Hyperthyroidism causes sustained high plasma concentrations of T4 and T3.

• There is often generalized increase in the metabolic rate, evidenced clinically by, for example, heat intolerance, a fine tremor, tachycardia including atrial fibrillation, weight loss, tiredness, anxiety, sweating and diarrhoea

• biochemical features Hypercalcaemia is occasionally found in patients with severe thyrotoxicosis. There is an increased turnover of bone cells, probably due to a direct action of thyroid hormone.
Hypocholesterolaemia can occur, due to increased LDL clearance.
● Hypokalaemia may also occur, associated with hyperthyrotoxic periodic paralysis.
● Plasma SHBG is increased.
● Plasma creatine kinase may be increased with thyrotoxic myopathy
• Graves' disease This is the most common form of thyrotoxicosis and occurs more often in females than in males. It may be caused by relatively autonomous secretion from a diffuse goitre and is characterized by:
● exophthalmos, due to lymphocytic infiltration and swelling of retro-orbital tissues of the eyes
● sometimes localized thickening of the subcutaneous tissue over the shin (pretibial myxoedema).
• Graves' disease is an autoimmune thyroid disease characterized by a variety of circulating antibodies, including anti-TPO, as well as being associated with other autoimmune diseases such as type 1 diabetes mellitus, adrenal insufficiency and pernicious anaemia. Thyroid antibodies are detectable in some cases, such as thyroid-stimulating immunoglobulin (TSI), which is directed towards epitopes of the TSH receptor and thus acts as a TSH receptor agonist. Nuclear medicine tests may show a high radioactive uptake of iodine by the thyroid gland.
• subacute thyroiditis :This is a destructive thyroiditis resulting in the release of preformed thyroid hormones. Thereare three subtypes:
• granulomatous or painful, lymphocytic or silent and painless, and post-partum. This condition is associated with extremely elevated thyroid hormones and no radioactive iodine uptake by the thyroid gland.

• The clinical course progresses through 6–8 weeks of thyrotoxicosis, 2–4 months of hypothyroidism and a return to euthyroidism in about 90 per cent of patients.
• The painful or granulomatous variety is thought to be a viral disease and is associated with human leucocyte antigen (HLA)-Bw35.
• The lymphocytic variety is autoimmune, as is post-partum Treatment is supportive, as in many cases the condition is self-limiting.
• Toxic nodules: either single or multiple, in a nodular goitre may secrete thyroid hormones autonomously. The secretion of TSH is suppressed by negative feedback, as in Graves' disease. The nodules may be detected by their uptake of radioactive iodine or technetium, with suppression of uptake in the rest of the thyroid tissue ('hot nodules').
• Toxic nodules are found most commonly in older patients, who may present with only one of the features of hyperactivity, usually cardiovascular symptoms such as atrial fibrillation. Toxic multinodular goitre is also called Plummer's disease.
• Rare hyperthyroid states
1-Jod–Basedow syndrome is hyperthyroidism in patients with excess iodide intake, for example from the diet or from iodine-containing contrast medium. High iodine intake may be assessed by urinary iodide assay.
2-Metastatic thyroid carcinoma can produce thyroid hormones.
3- In struma ovarii, ectopic thyroid tissues found in ovarian teratomas
4- Patients with choriocarcinoma or molar hydatidi form pregnancy have extremely high concentrations of b-human chorionic gonadotrophin that can activate.
• 5- the TSH receptor. Rarely, the pituitary tumour releases TSH, resulting in thyrotoxicosis. Pathophysiology of hyperthyroidism Plasma T4 or fT4 and T3 and fT3 concentrations are usually increased in hyperthyroidism.

• Much of the T3 is secreted directly by the thyroid gland, and the increase in plasma T3 concentrations is greater, and usually evident earlier, than that of T4.
• Rarely, only plasmaT 3 and fT3 concentrations are elevated (T3 toxicosis). In both situations, TSH secretion is suppressed by negative feedback, and plasma TSH concentrations are either very low or undetectable.
• Treatment: Various forms of treatment are available, the selection of which depends on the
• 1- cause
2- the clinical presentation '
3- age of the patient.
• b-blocker drugs such as propranolol, which inhibit the peripheral conversion of T4 to T3, may be used initially.
• Additional treatment includes the use of such drugs as carbimazole or propylthiouracil.
• Carbimazole inhibits the synthesis of T3 and T4;
• propylthiouracil additionally inhibits T4 to T3 conversion.
• Some clinicians use block-and-replace regimens: carbimazole is used to 'block' thyroid secretion, and simultaneous exogenous T4 maintains and replaces T4 concentrations.
It is important to remember that carbimazole can have the potentially lethal side effect of bone marrow suppression, and patients should be warned about infections such as sore throats and about the need to have their full blood count monitored.
2- Radioactive iodine can be used in resistant or relapsing cases;
surgery is rarely indicated, but may have a place if there is a large toxic goitre that is exerting pressure or if drug therapy fails but radioactive iodine is contraindicated.
• Thyroid function must be checked regularly, as some patients may become hypothyroid or may relapse after radioiodine or surgery

• Subclinical hyperthyroidism : may occur with a low or suppressed TSH concentration but normal (usually high-normal) plasma fT4 and fT3 concentrations.
• The condition may progress to full-blown hyperthyroidism with suppressed plasma TSH and raised plasma fT4 and fT3 concentrations.
• Subclinical hyperthyroidism may be associated with atrial fibrillation, decreased bone mineral density and other features of hyperthyroidism. Plasma TSI may be raised.
• aboratory investigation of suspected hyperthyroidism A careful history (including drugs) should be taken and examination performed, checking for a goitre.
• The plasma TSH, fT3 and fT4 concentrations should be measured.
● The plasma fT4 and fT3 concentrations are clearly high and the TSH concentration is suppressed in clinically thyrotoxic patients.
● In the face of suppressed plasma TSH, a clearly elevated plasma fT3 concentration confirms the diagnosis of hyperthyroidism. Remember that in T3 thyrotoxicosis the plasma fT4 may be normal.
• f the plasma fT4 concentration is raised and the TSH concentration is normal, this is suggestive of biochemical euthyroid hyperthyroxaemia
• Measurement of thyroid antibodies is useful, particularly if the concentration of TSIs is raised, which supports a diagnosis of Graves' disease.
• The rare TSH-secreting pituitary tumours need pituitary assessment a-subunit concentrations may be useful, as they are usually raised in such circumstances.
• In difficult cases, determination of plasma SHBG concentration can help decide whether the patient is hyperthyroid, as it is lowered in hypothyroidism and raised in hyperthyroidism.
● Radioiodine uptake studies of the thyroid can be useful to distinguish some of the causes of hyperthyroidism
● The TRH test is sometimes useful in the diagnosis of unclear cases.

• Euthyroid goitre If plasma T4 concentrations fall, enlargement of the thyroid gland (goitre) may be caused by TSH stimulation resulting in cellular hyperplasia.
• Thyroxine synthesis may be impaired by iodide deficiency, caused by drugs such as para-aminosalicylic acid, or possibly by partial deficiency of the enzymes involved in T4 synthesis. Under the influence of prolonged stimulation by TSH, the number of thyroid cells increases and plasma thyroid hormone concentrations are maintained at the expense of the development of a goitre.
• Inflammation of the thyroid gland (thyroiditis), whether acute or subacute, may produce marked but temporary aberrations of thyroid function tests.
• Ultrasound scanning can be useful in the diagnosis of goitre, as can radiolabelled uptake studies to see if there are hot (T4-producing) or cold (nonproducing) nodule(s).
• Sick euthyroid': Any severe illness may be associated with low plasma total or fT4 concentrations and may make the interpretation of thyroid function tests extremely difficult.
• Plasma TSH concentrations may be normal or slightly high or low. The TSH response to TRH may also be impaired. There may be impaired conversion of T4 to T 3 with low plasma T3 concentrations. Consequently, the assessment of thyroid function is best deferred until the patient has recovered from the illness.
• Euthyroid hyperthyroxinaemia: This is defined as a condition in which either the plasma total or fT4 concentration is abnormally raised without clinical evidence of thyroid disease.
• These changes may be transient or persistent, with high, normal or low total or fT 3 concentrations.
• Heterophilic antibodies to fT4 and/or fT3 should be excluded [these can sometimes be removed by the laboratory by treating the sample with polyethylene glycol (PEG), which can precipitate these antibodies], as they can interfere with some assays.
• Causes

● Physiological conditions resulting in raised plasma TBG concentration, for example pregnancy. Concentrations of total T 4and T3are both elevated, but there are usually normal fT4 and fT3 concentrations.
● TBG concentration is raised in newborn babies.
● Hereditary causes: – hereditary TBG excess is X-linked, – hereditary transthyretin excess,
• familial dysalbuminaemic hyperthyroxinaemia, (FDH) due to an abnormal form of albumin.
● Drugs causing hyperthyroxinaemia fT4: – estrogens raise TBG concentration, as do 5-fluorouracil, heroin and methadone, – amiodarone blocks conversion of T4 to T3, resulting in an elevation of T4 and reverse T3 concentrations, – heparin, due to fatty acid release, inhibits fT4 binding to TBG, – propranolol inhibits extrathyroidal conversion of T4 to T3,
• Some patients with certain illnesses, for example hyperemesis gravidarum, have low total and fT3 concentrations due to reduced peripheral conversion of T4 to T3 because 5-deiodinase is inhibited.
• This results in elevated total T4 and fT4 concentrations. Some hepatic disorders, including acute hepatitis, result in raised concentrations of TBG and T4 andfT4.
• In up to 10 per cent of cases of acute psychosis,total and fT4 concentrations are raised. The exact mechanism is unknown, but it may be due to central activation of the hypothalamic–pituitary axis.

• Amiodarone and thyroid function Amiodarone is sometimes used to treat certain cardiac arrhythmias. This drug can evoke hypothyroidism, partly because it interrupts the conversion of T4 to T3. However, it contains iodine and can also evoke thyrotoxicosis by the Jod–Basedow or type 1 phenomenon. Conversely, it may elicit disruptive thyroiditis and thyrotoxicosis with raised interleukin-6 concentration (type 2 phenomenon).
• The drug has along half-life (40–100 days) and thus takes a long time to clear from the body.

• TRATEGY FOR THYROID FUNCTION TESTING AND INTERPRETATION ● A first-line test for thyroid function (as stated above) is plasma TSH, although this can be difficult to interpret in the absence of fT4.

● If the plasma TSH concentration is *normal* and the patient is clinically euthyroid, look at plasma fT4: – If fT 4concentration is low, consider sick euthyroid/ non-thyroidal illness, certain drugs, such as carbamazepine or phenytoin. – If fT4 concentration is also normal, thyroid function is likely to be normal

• If fT4 concentration is high, consider euthyroid hyperthyroxinaemia, interfering assay autoantibodies.

● If the plasma TSH concentration is *low*, look at plasma fT4: – If fT4 concentration is low, consider sick euthyroid/non-thyroid illness, pituitary or hypothalamic disease (secondary hypothyroidism?), certain drugs. – If fT4 concentration is normal, consider sick euthyroid/non-thyroid illness, **subclinical hyperthyroidism,** particularly if clinically hyperthyroid, certain drugs, such as glucocorticoids and dopamine that may affect TSH, fT3 toxicosis (fT3 concentration is raised).

– If fT4 concentration is high, consider hyperthyroidism, drugs such as amiodarone , iodine excess, hyper emesis gravidarum, molar pregnancy, activating TSH receptor mutations.

• if the plasma TSH concentration is *high*, look at plasma fT4:

– If fT 4 concentration is low, consider primary hypothyroidism .

– If fT 4 concentration is normal, consider compensated hypothyroidism, drugs such as metoclopramide or domperidone, or sick euthyroid.

– If fT4 concentration is high, consider generalized thyroid hormone resistance, TSH secreting tumour, tinterfering assay antibodies.

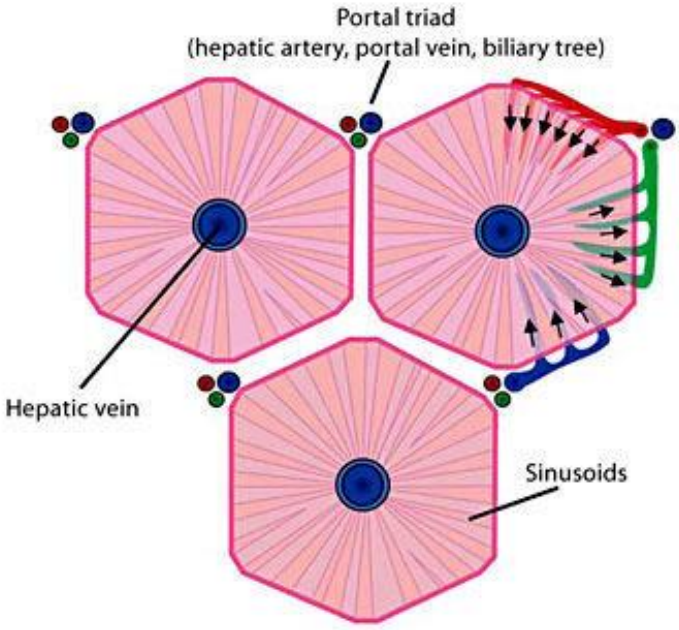
CHAPTER 3

LIVER

• **FUNCTIONS OF THE LIVER**

• 1- The liver has essential synthetic and excretory functions and can be thought of as a large ‘metabolic factory’.

• 2- It also detoxifies and, like the kidneys, excretes the end products of metabolism.



• The main blood supply to the liver is via the portal vein. The liver is made up of hexagonal lobules of cells. Rows of hepatocytes radiate from the central hepatic vein and are separated by sinusoidal spaces, along the walls of which are interspersed hepatic macrophages, the Kupffer cells. These phagocytic cells
are part of the reticulo endothelial system and have an Important detoxifying function.

● Hypoxia and toxins that are metabolized in the liver cause damage to the centrilobular area first.

● Toxins that do not depend on hepatic metabolism primarily affect the periphery of the lobule. Almost all nutrients from the gastrointestinal tract pass through the sinusoidal spaces prior to entering the systemic circulation.

• The hepatic architecture may be disturbed in cirrhosis (fibrosis).

• 1- General metabolic functions When the glucose concentration is high in the portal vein, it is converted to glycogen and the carbon skeletons of fatty acids, which are transported to adipose tissue as very low-density lipoprotein (VLDL).

• During fasting, the systemic plasma glucose concentration is maintained by the breakdown of glycogen (glycogenolysis) or by the synthesis of glucose from substrates such as glycerol, lactate and amino acids (gluconeogenesis).

• Fatty acids reaching the liver from fat stores may be metabolized in the tricarboxylic acid cycle, converted to ketones or incorporated into triglycerides

• 2- Synthetic functions Hepatocytes synthesize:

● *plasma proteins*, excluding immunoglobulins and complement,

● most *coagulation factors*, including fibrinogen and factors II (prothrombin), V, VII, IX, X, XI, XII and XIII – of these, prothrombin (II) and factors VII, IX and X cannot be synthesized without vitamin K,
● *primary bile acids*
● the *lipoproteins*, such as VLDL and high-density lipoprotein (HDL)
• a fall in plasma albumin concentration is attributed to advanced liver disease,
• Prothrombin levels, assessed by measuring the prothrombin time, may be reduced because of impaired hepatic synthesis,
• If hepatocellular function is adequate, parenteral administration of vitamin K may reverse the abnormality
• **Excretion and detoxification are liver include the following:**
● *Cholesterol*
● *Amino acids* .
● *Steroid hormones* – which are metabolized and inactivated by conjugation with glucuronate and sulphate and excreted in the urine in these water soluble forms.
• Many *drugs* some are excreted in the bile.
● *Toxins* – the reticuloendothelial Kupffer cells.
Efficient excretion of the end products of metabolism and of bilirubin depends on:
● normally functioning liver cells, ● normal blood flow through the liver
● patent biliary
●Formation and excretion of bilirubin
At the end of their lifespan, red blood cells are broken down by the reticuloendothelial system, mainly in the spleen. **ممكن يجيب السبلين امسكيو**
• The released haemoglobin is split into globin, which enters the general protein pool, and haem, which is converted to bilirubin after the removal of iron, which is reused .
About 80 per cent of bilirubin is derived from haem
• Bilirubin is normally transported to the liver bound to albumin. unconjugated bilirubin.
• In this form it is potentially toxic; however, at physiological concentrations it is all protein bound. In the adult, about 300 µmol per day of bilirubin reaches the liver, where it is transferred from plasma albumin, through the permeable vascular sinusoidal membrane.
•. Bilirubin is bound to ligandin (Y protein). From there it is actively transported to the smooth endoplasmic reticulum, where it is conjugated with glucuronate by a process catalysed by uridine diphosphate glucuronyl transferase..

• These energy-dependent steps are the ones most likely to be impaired by liver damage (hypoxia and septicaemia)
• Novobiocin inhibits glucuronyl transferase.
● An increased rate of bilirubin production exceeds normal excretory capacity of the liver (prehepatic jaundice).
● the normal load of bilirubin cannot be conjugated and/or excreted by damaged liver cells (hepatic jaundice).
● the biliary flow is obstructed, so that conjugated bilirubin cannot be excreted into the intestine and is regurgitated into the systemic circulation (posthepatic jaundice).
• Retention of bilirubin in plasma:
• Jaundice unconjugated hyperbilirubinaemia occurs if there is:
● a marked increase in the bilirubin load as a result of haemolysis, or of the breakdown of large amounts of blood after haemorrhage
● impaired binding of bilirubin to ligandin or impaired conjugation with glucuronate in the liver.
• In addition, the proportion of unbound, unconjugated bilirubin, and therefore the risk of cerebral damage, increases if:
● plasma albumin concentration is low,
● Unconjugated bilirubin is displaced from binding sites, by free fatty acids or drugs such as salicylates or sulphonamides.
• Unconjugated bilirubin is normally all protein bound and is not water soluble and therefore cannot be excreted in the urine.
• Patients with unconjugated hyperbilirubinaemia do not have bilirubinuria (‘acholuric jaundice’) such as Gilbert’s syndrome. In most cases of jaundice in adults,
• Conjugated bilirubin is water soluble and is less strongly protein bound than the unconjugated form, and therefore can be excreted in the urine.
• Urobilinogen, unlike bilirubin, is often detectable in the urine of normal people by testing with commercial strip tests, particularly if the urine, and therefore the urobilinogen, is concentrated.
• Urinary urobilinogen concentration is increased in the following situations.
1- When haemolysis is very severe
2- When liver damage impairs re-excretion of normal amounts of urobilinogen into the bile.

• BIOCHEMICAL TESTS FOR LIVER DISEASE

• A rise aminotransferase cytoplasmic and/ or mitochondrial membranes damage

• Liver cells contain more aspartate aminotransferase (AST) than alanine aminotransferase (ALT)Raised plasma transaminase concentrations are indicative of hepatocyte damage,and infiltrative disorders
• In inflammatory or infective conditions, such as viral hepatitis,.. causes a greater increase ALT than AST activities. .
AST may be present in skeletal muscle and is more sensitive than ALT.
• A plasma AST:ALT ratio of > 2 is suggestive but not diagnostic of alcoholic liver disease and a ratio < 1 suggests chronic viral hepatitis or hepatic steatosis

Hepatic synthetic function:

• Albumin Hypoalbuminaemia is such a common finding in many severe illnesses that it is a less specific indicator of impaired synthetic capacity than a prolonged prothrombin time..
• Prothrombin time: The prothrombin time may be prolonged by cholestasis: fat-soluble vitamin K cannot be absorbed normally if fat absorption is impaired due to intestinal bile salt deficiency.
• A high plasma conjugated bilirubin concentration indicates impaired hepatic excretory function
• *Alkaline phosphatase* including the liver, the osteoblasts in bone and the placenta. Plasma activities rise in cholestatic liver disease because ALP synthesis is increased and the enzyme within the biliary tract is regurgitated into plasma.

Type of liver damage:

● **Cholestasis** is characterized by retention of conjugated bilirubin and of ALP, and by increased ALP synthesis at the sinusoidal surface. Plasma conjugated bilirubin levels and ALP activities are increased.
• *Urine Multistix* include bilirubin to form azobilirubin. Drugs, such as large doses of chlorpromazine,may give false-positive results.
This test will detect **urobilinogen** in urine False-positive drugs such as para-aminosalicylic acid and some sulphonamides.
• galactose elimination capacity, the aminopyrine breath test, indocyanine green clearance, and monoethylglycinexylidide (MEGX) production. انواع اختبارات وضائف الكبد الجديدة الجديدة
• All these tests are indirect measures of hepatic activity سؤال شنو الانداير كت اندكيتر للفر فنكشن
• **Cholestasis** may be either: ● *intrahepatic*, in which bile secretion from the hepatocytes into the canaliculi is impaired, due to: – viral hepatitis, – drugs such as chlorpromazine or toxins such as alcohol, – inflammation of the biliary tract (cholangitis), – autoimmune disease (primary biliary cirrhosis), – cystic fibrosis,

• *extrahepatic*, due to obstruction to the flow of bile through the biliary tract by: – biliary stones, – inflammation of the biliary tract, – pressure on the tract from outside by malignant tissue, usually of the head of the pancreas, – biliary atresia (rare).
The biochemical findings may be similar Bilirubin concentrations in plasma may be normal if only part of the biliary system is involved by intrahepatic lesions such as cholangitis,
• Alkaline phosphatase activity is a sensitive test for cholestasis. Increased synthesis of ALP in theaffected ducts increases the activity o
• Patients with prolonged and more widespread cholestasis may present with severe jaundice and pruritus due to the deposition of retained bile salts in the skin.
• More rarely, there is bleeding due to malabsorption of vitamin K, with consequent prothrombin deficiency.
• Cholesterol retention may cause hypercholesterolaemia. Dark urine and pale stools suggest biliary retention of conjugated bilirubin.
• The jaundice caused by extrahepatic obstruction due to malignant tissue is typically painless and progressive, but there may be a history of vague persistent back pain and weight loss.
• By contrast, intraluminal obstruction by a gallstone may cause severe pain, which, like the jaundice, is often intermittent
• Gallstones may not always cause such symptoms. If a large stone lodges in the lower end of the common bile duct,
• Unless the cause is clinically obvious, evidence of dilated ducts due to extrahepatic obstruction should be sought using tests such as ultrasound, computerized tomography (CT) scanning or cholangiography.
• Destruction and proliferation of the bile ducts produce a predominantly cholestatic picture, with pruritus and a plasma ALP activity that may be very high. Jaundice develops late in most patients.
• Prolonged parenteral nutrition may be associated with a progressive increase in plasma ALP activity and AST
• Viral hepatitis may be associated with (Epstein–Barr virus), rubella and cytomegalovirus.
: *Hepatitis A* (‘infectious hepatitis’), transmitted by the faecal–oral route as a food-borne infection incubation period of between 15 and 45 days. Relapses may occur, but it rarely progresses to chronic hepatitis.
• *Hepatitis B* (‘serum hepatitis’) is transmitted by blood products and other body fluids; longer incubation period, of between 40 and 180 days

● *Hepatitis C* (non-A, non-B hepatitis), which may be the result of sexual transmission or the transfusion of blood products, has an incubation period of between 15 and 50 days. It may progress to cirrhosis.
• Testing for viral antigens, or for antibodies synthesized in response to the virus,
• Anti-HCV anti-bodies may be detected in plasma about 12 weeks after exposure to the virus in about 50 per cent of patients.
It should be noted that there are other possible viruses that can cause liver dysfunction such as hepatitis D and E.
• Hepatitis D is a ribonucleic acid (RNA) subviral satellite commonly by the oral–faecal route.

Chronic persistent hepatitis:

raised plasma aminotransferase activities without clinical signs or symptoms and without a significant change in activity over many years.
● be associated with, or a consequence of, viral infections such as HBV or HCV, or may be drug induced,
● be part of an autoimmune process that sometimes involves more than one organ
● have no obvious cause.

.**Cirrhosis:**

• Cirrhosis is the end result of many inflammatory and metabolic diseases involving the liver, including prolonged toxic damage, usually due to alcohol.
• In 'cryptogenic cirrhosis', the cause is unknown.
• The fibrous scar tissue distorts the hepatic architecture, and regenerating nodules of hepatocytes disrupt the blood supply, sometimes increasing the pressure in the portal vein, causing portal hypertension.
• the plasma AST, and sometimes ALT, activities rise.
• Portal hypertension and impaired lymphatic drainage lead to the accumulation of fluid in the peritoneal cavity (ascites). This may be aggravated by hypoalbuminaemia, which may also cause peripheral oedema.
• In advanced cirrhosis, the findings of hepatocellular failure develop. There are a number of causes of ascites including cirrhosis, malignancy or infection, nephrotic syndrome, hypothyroidism, pancreatitis and cardiac failure.

Hepatocellular failure and hepatic encephalopathy:

• liver damage severe enough to cause obvious clinical signs of impaired hepatocellular function may be caused by severe hepatitis or advanced cirrhosis, or may follow an overdose of a liver toxin such as paracetamol (acetaminophen).
• The biochemical findings may include any or all of those of acute hepatitis. Jaundice is progressive. In the final stage, the number of hepatocytes, and so the

total amount of aminotransferases released, may be so reduced that plasma activities fall despite continuing damage to the remaining cells.

• This finding should not be interpreted as a sign of recovery

• Other features may include the following:

● Hypovolaemia and hypotension, which are due to loss of circulating fluid in ascites and in the edema fluid formed because of hypoalbuminaemia, and which may be aggravated by vomiting.

• increased antidiuretic hormone (ADH) and secondary hyperaldosteronism, causing electrolyte disturbances, especially hypokalaemia, and sometimes dilutional hyponatraemia. – renal circulatory insufficiency, causing oliguria, a high plasma creatinine concentration and uraemia despite reduced urea synthesis.

● Impaired hepatic deamination of amino acids, causing accumulation of amino acids in plasma with over flow amino aciduria and sometimes hyperammonaemia.

● Impairment of hepatic gluconeogenesis may cause hypoglycaemia.

Treatment of end-stage liver disease:

• Liver transplantation may be the only possible treatment for end-stage liver disease.

• Complications include graft failure, hepatic artery thrombosis, infection and acute and chronic rejection.

The indications for hepatic transplantation may include prolonged prothrombin time and plasma bilirubin more than 300 µmol/L.

Hepatic infiltration and malignant disease:

• invasion of the liver by secondary carcinoma, or infiltration by lymphoma or granulomas such as sarcoidosis, may be associated with abnormal biochemical tests.

Metabolic liver disease:

• A group of rare metabolic disorders, most of which are inherited, is associated with liver disease, especially cirrhosis

• α 1-Antitrypsin deficiency α1-Antitrypsin deficiency is associated with neonatal hepatitis in individuals with the PiZZ phenotype

• Galactosaemia This autosomal recessive disorder, due most commonly to a deficiency of galactose-1-phosphate uridyltransferase, may cause cirrhosis of the liver if untreated.

• Wilson's disease This is a rare, recessively inherited disorder caused by reduced biliary excretion of copper and by impaired hepatic incorporation of copper into caeruloplasmin.

Reye's syndrome:

• This rare disorder presents as acute hepatitis, associated with marked encephalopathy, severe metabolic acidosis and hypoglycaemia in children typically between the ages of 3 and about 12 years.
• There is acute fatty infiltration of the liver. The plasma aminotransferase activities are high, but plasma bilirubin levels are only slightly raised. The aetiology is uncertain, but the condition may be precipitated by viral infections, such as influenza A or B, drugs such as salicylates and sodium valproate, and certain toxins; it has been recommended that children should not be given aspirin. One possible mechanism is that there is uncoupling of mitochondrial oxidative phosphorylation.

Non-alcoholic steatotic hepatitis or fatty liver:

• Non-alcoholic fatty liver disease (NAFLD) refers to a spectrum of liver disease ranging from fatty liver (steatosis) to non-alcoholic steatotic hepatitis (NASH)
• Hepatorenal syndrome: This syndrome occurs when cirrhosis and often portal hypertension presents in conjunction with renal dysfunction.
• It is thought to be due to impaired renal perfusion due to vasoconstriction of renal arteries. Usually the creatinine clearance is less than 40 mL/min and plasma

JAUNDICE:

• Haemolytic jaundice: There are many causes of haemolysis, including sicklecell anaemia, thalassaemia and spherocytosis, and it can also be drug or autoimmune induced.
• In adults, unconjugated hyperbilirubinaemia is usually mild because of the large reserve of hepatic secretory capacity.
• The plasma bilirubin concentration is usually less than 70 µmol/L. Erythrocytes contain high amounts of AST and lactate dehydrogenase (LDH1 and LDH2).
The inherited hyperbilirubinaemias:
• Unconjugated hyperbilirubinaemia *Gilbert's syndrome:* This is a relatively common (3–7 per cent of the population) familial condition, which may be present at any age but usually develops after the second decade.
• Hepatic UGT activity is decreased to approximately 30 per cent of normal in individuals with Gilbert's syndrome. Decreased activity has been attributed to an expansion of thymine–adenine repeats in the promoter region of the *UGT1A1* gene, the principal gene encoding this enzyme.
• Diagnosis of Gilbert's syndrome is by exclusion of haemolysis and other hepatic disorders.

Crigler–Najjar syndrom:

• This is due to a rare deficiency of hepatic UGT, It usually presents at birth. The plasma unconjugated bilirubin may increase to concentrations that exceed the

binding capacity of albumin and so cause kernicterus. The defect may be *complete* (type I), and inherited as an autosomal recessive condition, or *partial* (type II),

Conjugated hyperbilirubinaemia:

• *Dubin–Johnson syndrome:* This is probably harmless and is due to defective excretion of conjugated bilirubin, but not of bile acids. It is characterized by slightly raised plasma conjugated bilirubin levels that tend to fluctuate.

• The diagnosis may be obtained by liver biopsy.

• *Rotor's syndrome:* is similar in most respects to Dubin– Johnson syndrome, but the liver cells are not pigmented.

BILE AND GALLSTONES:

• Bile acids and bile salts: Four bile acids are produced in humans. Two of these, cholic acid and chenodeoxycholic acid, are synthesized in the liver from cholesterol and are called primary bile acids.

• They are secreted in bile as sodium salts, conjugated with the amino acid glycine or taurine (primary bile salts). These are converted by bacteria within the intestinal lumen to the secondary bile salts, deoxycholate and lithocholate, respectively . Secondary bile salts are partly absorbed from the terminal ileum and colon and are re-excreted by the liver (enterohepatic circulation of bile salts).

• Therefore, bile contains a mixture of primary and secondary bile salts. Deficiency of bile salts in the intestinal lumen leads to impaired micelle formation and malabsorption of fat.

Cholesterol gallstones:

• Cholesterol is most likely to precipitate if bile is supersaturated with it; further precipitation on a nucleus of crystals causes progressive enlargement. Not all patients with a high biliary cholesterol concentration suffer from bile stones.

• Changes in the relative concentrations of different bile salts may favour precipitation. The stones may be single or multiple.

• They are described as mulberry-like and are either white or yellowish; the cut surface appears crystalline..

• fibric acid derivatives. يزيد الكل ستون

● *Chronic cholecystitis* may also be associated with gallstones. ● *Obstruction of the common bile duct* occurs if a stone lodges in it. The patient may present with biliary colic, obstructive jaundice , which isusually intermittent, or acute pancreatitis if the pancreatic duct is also occluded. ● Rarely, gallstones may be associated with *gallstone ileus* or *carcinoma of the gall bladder*.

● In obstructive jaundice (biliary obstruction), the plasma ALP is usually more than four to five times and GGT more than 10 times normal.
• Liver/biliary ultrasound is useful to distinguish between obstructive jaundice with dilated biliary ducts or undilated ducts.

Suspected liver disease showing abnormal plasma hepatic enzymes:

• Relevant points in the clinical evaluation are: – a previous history of hepatitis, intravenous drug use, occupational and sexual history, – alcohol intake and medication history, for example paracetamol, – the presence, or history, of other autoimmune disorders, – jaundice, pruritus or features of malabsorption, – family history of liver disease. .
– A high plasma ALP activity with raised GGT concentration suggests cholestasis. – Aminotransferase levels of more than 10 times normal suggest primary hepatocyte damage.
• A low plasma albumin concentration (hypoalbuminaemia) in the face of abnormal liver function tests can be seen in cirrhosis implying chronicity.
● A prolonged prothrombin time implies poor hepatic synthetic capacity, for example clotting factors, and is prognostic in paracetamol overdose.
• It is also important if a liver biopsy is considered.
● Significant infiltration of the liver by tumour cells, or by granulomas such as sarcoidosis
● A fatty liver may be revealed by liver ultrasound as this may show increased echogenicity. This may be associated with hyper triglyceridaemia, obesity and type 2 diabetes mellitus or impaired glucose regulation. ● If primary hepatocellular carcinoma is suspected, the plasma a-fetoprotein level may also be high. ● Low plasma copper and caeruloplasmin concentrations may suggest Wilson's disease , and plasma a1-antitrypsin deficiency can result in cirrhosis . ● Radionuclide scans or other imaging procedures (CT or MRI) may be useful. A liver biopsy may be indicated to clarify a histological diagnosis

CHAPTER 4

Inborn errors of metabolism

The inherited characteristics of an individual are determined by about 50 000 gene pairs, arranged on 23 pairs of chromosomes, one of each pair coming from the father and one from the mother.

inborn errors of metabolism (IEM). Incidences of IEM range from about 1 in 100 to 1 in 200 000, depending on the disorder and the population involved

SOME METABOLIC CONSEQUENCES OF GENETIC DEFECTS:

• Inherited inborn disorders may involve any peptide or protein, and are usually most obvious if there is an enzyme abnormality. Deficiency of a single enzyme

for example congenital adrenal hyperplasia when accumulation of androgens causes virilization

CLINICAL IMPORTANCE OF INBORN ERRORS OF METABOLISM

Some inborn errors are probably harmless. However, they are important because they produce effects that may lead to misdiagnosis, for example renal glycosuria and Gilbert's syndrome.

NEONATAL SCREENING

The criteria should depend on the following characteristics of the disorder or of the test:

● The disease should not be clinically apparent at the time of screening and should have a relatively high incidence in the population screened.

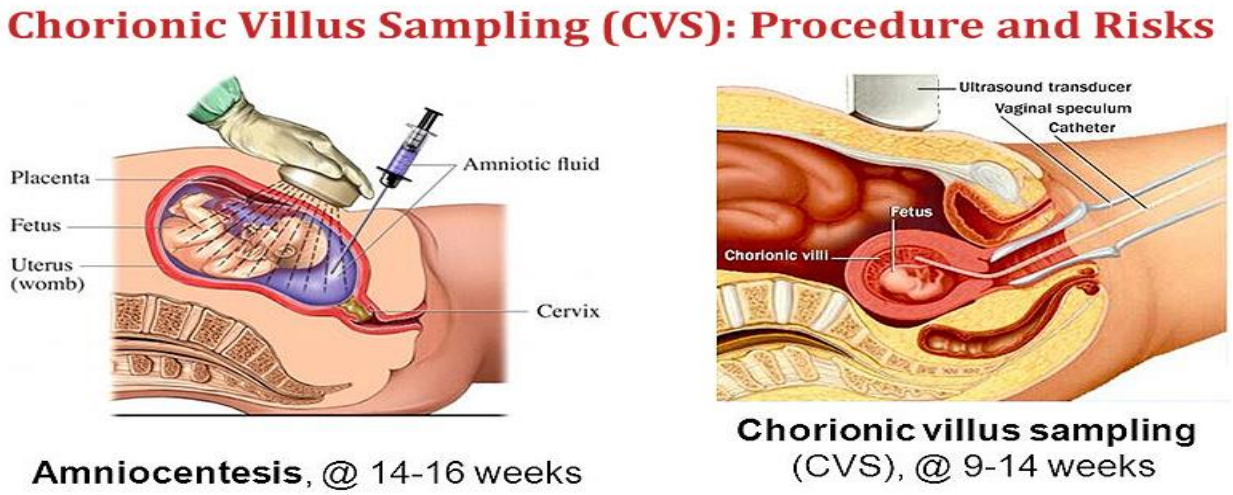
● The disease should be treatable or early treatment should improve outcome.

● It must be possible to obtain the result of the screening test before irreversible damage is likely to have occurred.

● The screening test should be simple and reliable and the cost of the programme should, ideally, be at least partly offset by the cost savings resulting from early treatment. For example, such treatment may sometimes eliminate the need for prolonged institutional care. Not all these criteria are necessarily fulfi lled in all screening programmes. In the UK, at between 5 and 8 days, babies are screened for certain conditions by taking a small capillary blood sample from a heel prick (see Chapter 26, Fig. 26.2). Blood spots are placed on a paper card, which can be posted to the regional laboratory for assay. In the UK,. Other conditions that may be screened for in certain regions The use of deoxyribonucleic acid (DNA) technology and tandem mass spectroscopy in antenatal screening can be expected to increase in the future.

PRENATAL SCREENING

of high-risk groups only, may be performed for some disorders in order to plan



Prenatal screening for inherited metabolic disorders most commonly involves demonstrating the metabolic defect in cultured fetal fibroblasts obtained by amniocentesis early in the second trimester, or by chorionic villus sampling during the first trimester. Examples of those groups in whom such screening may be indicated include women with a previously affected infant and ethnic groups thought to have a relatively high incidence of the carrier state, such as of Tay–Sachs disease in Ashkenazi Jews. In these highrisk populations, screening is often performed before conception, enabling genetic advice and prenatal diagnosis to be offered to couples who are carriers. If, as in cystic fi brosis, the gene defect of the parent of an affected infant is known, there may be a case for selective screening of subsequent pregnancies using molecular biological techniques. Prenatal screening for congenital disorders, for example neural tube defects, or

chromosomal abnormalities may also be performed

Box 27.1 Some clinical findings suggestive of an inborn error of metabolism

Early
Hypoglycaemia
Metabolic acidosis
Failure to thrive
Vomiting
Fits or spasticity
Hepatosplenomegaly
Prolonged jaundice
A peculiar smell, or staining, of the nappies
Death of child in family and positive family history
Cataracts or retinitis pigmentosa

Late
Intellectual disabilities
Refractory rickets
Renal calculi
Neuropathy
Short stature
Dysmorphic features

Box 27.2 Possible laboratory investigation of a suspected inborn error of metabolism[a]

Full blood count
Serum electrolytes, bicarbonate and blood gases for acid–base status
Renal function tests, including plasma urea and creatinine
Liver function tests
Plasma ammonia
Blood glucose
Urine ketones
Serum cholesterol and triglyceride
Plasma lactate
Plasma uric acid
Thyroid function tests
Porphyrins

Further specialist tests
Plasma and sometimes urine amino acids
Urine orotic acid
Urine organic acids
Plasma carnitine
Metabolites in urine or plasma by tandem mass spectroscopy
Specific enzyme assays
DNA analysis of leucocytes or fibroblasts
Histological studies of affected tissue

[a]This is best carried out in conjunction with a specialist paediatric metabolic laboratory. Many patients present with at least one of the following: metabolic acidosis, hypoglycaemia or hyperammonaemia. The laboratory tests may include those listed above.

WHEN TO SUSPECT AN INBORN ERROR OF METABOLISM:

• Examples of indirect screening methods include:

● estimation of plasma ammonia concentration to test for disorders of the urea cycle or organic acidurias, in which it accumulates,

● chromatography of plasma and urine for amino acids for the detection of disorders of amino acid metabolism,

● detection of organic acids in urine in disorders of branched-chain amino acid metabolism and organic acidurias.

Genetic tests are being used more frequently, and their use is likely to increase still further.

PRINCIPLES OF TREATMENT OF INBORN ERRORS OF METABOLISM:

• Some inborn errors can be treated by:

● limiting the dietary intake of precursors in the affected metabolic pathway, such as phenylalanine in PKU or lactose in galactosaemia,

● supplying the missing metabolic product, such as cortisol in congenital adrenal hyperplasia,

● removing or reducing the accumulated product, such as ammonia in urea cycle disorders.
• Insertion of the missing or defective gene is being attempted for disorders

DISEASES DUE TO INBORN ERRORS OF METABOLISM:

• 1. urea cycle defects,

2. disorders of amino acid metabolism, for example amino acidurias,

3. lysosomal storage defects,

4. disorders of carbohydrate metabolism, for example glycogen storage disorders, gluconeogenesis and carbohydrate intolerance defects,

5. lipid, fatty acid oxidation defects and organic acidurias,

6. mitochondrial disorders,

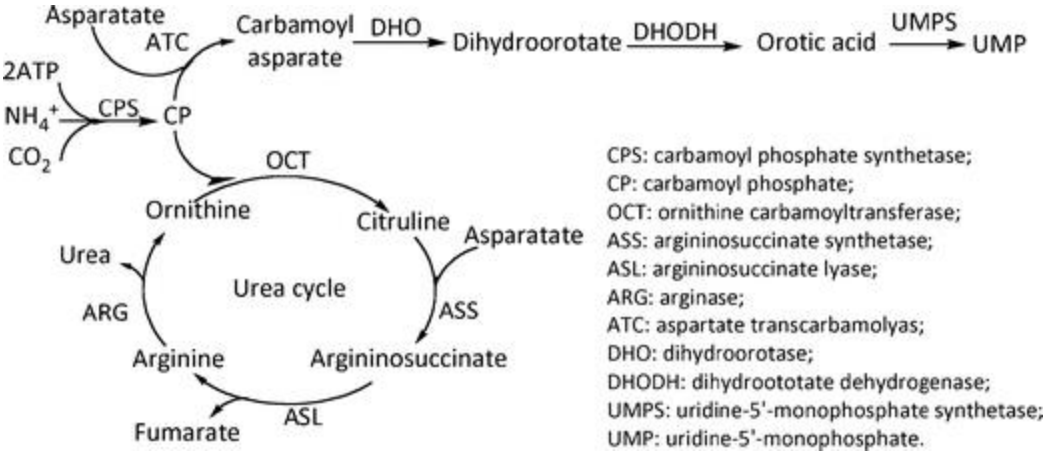
7. peroxisomal disorders,

8. abnormalities of drug metabolism,

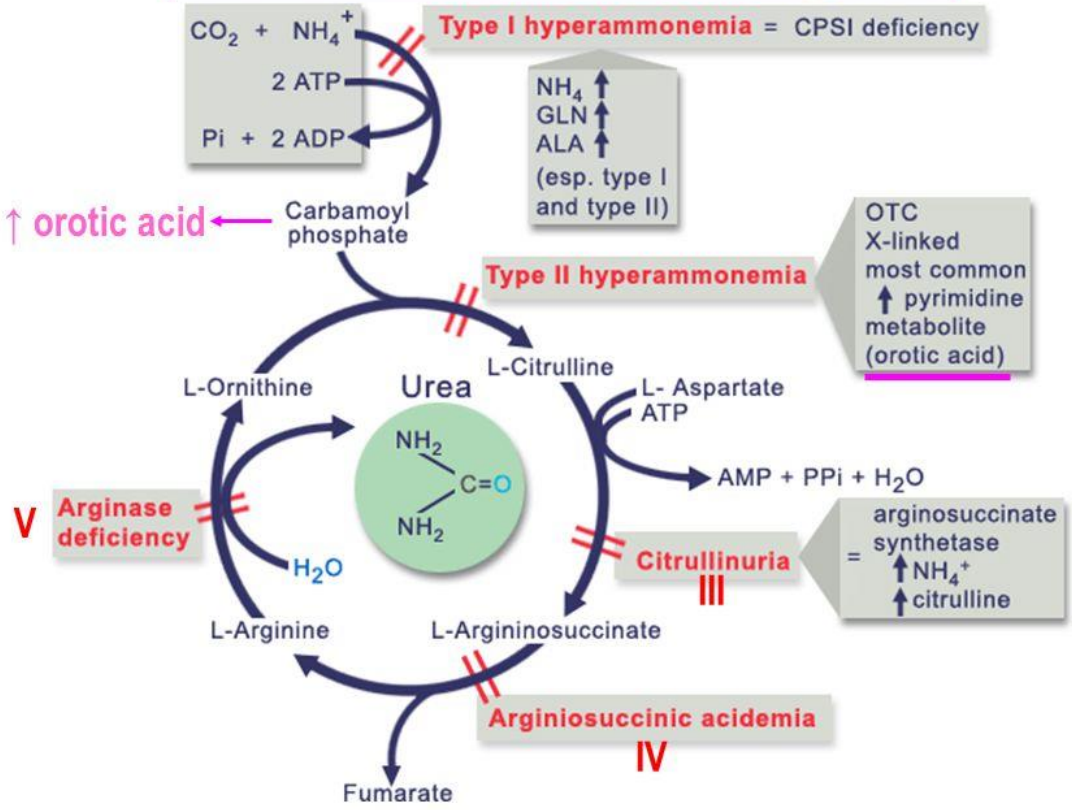
9. miscellaneous causes.

1 Urea cycle disorders:

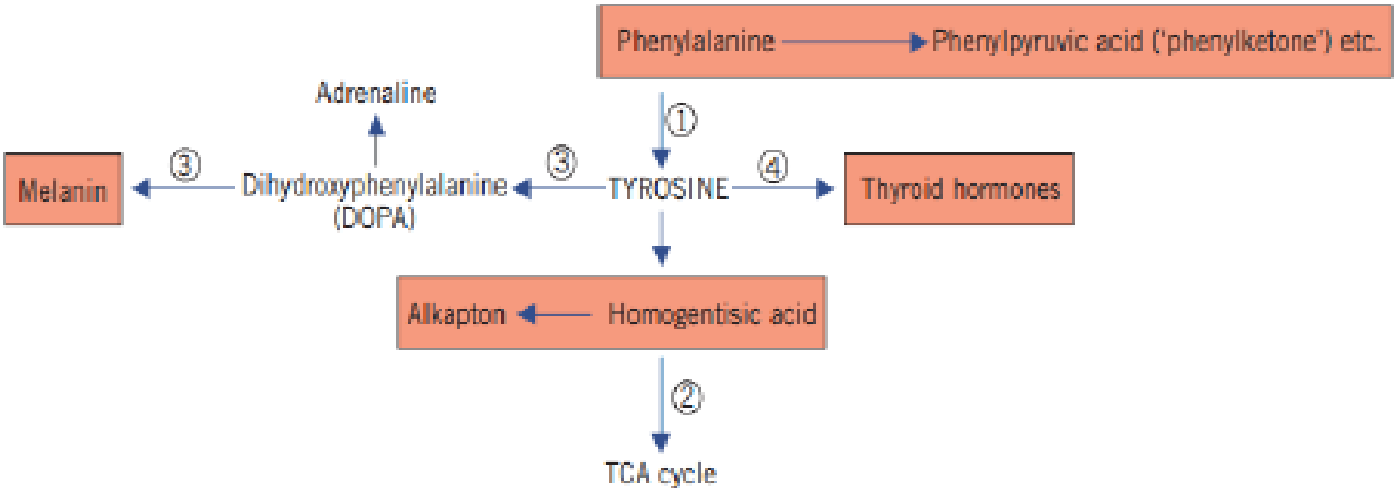
• Urea cycle defects are an important cause of hyperammonaemia and there may also be raised urinary orotic acid concentration, an intermediate metabolite of pyrimidine synthesis derived from carbamyl phosphate,
The urea cycle defects can present not only with severe hyperammonaemia, but also with a respiratory alkalosis and low plasma urea concentration .
Carbamyl phosphate synthetase (CPS) deficiency is a urea cycle disorder in which, unlike other defects in this pathway, urinary orotic acid is not raised.
Ornithine transcarbamylase deficiency is probably the most common urea cycle defect and is sex linked.



Defects of Urea Cycle



2 Disorders of amino acid metabolism:



Phenylketonuria:

The clinical features include:

● intellectual disabilities developing at between 4 and 6 months, with psychomotor irritability,

● a tendency to reduced melanin formation because of reduced production of tyrosine – many patients are pale skinned, fair haired and blue eyed,

● irritability, feeding problems, vomiting and fits during the first few weeks of life,

● often generalized eczema.

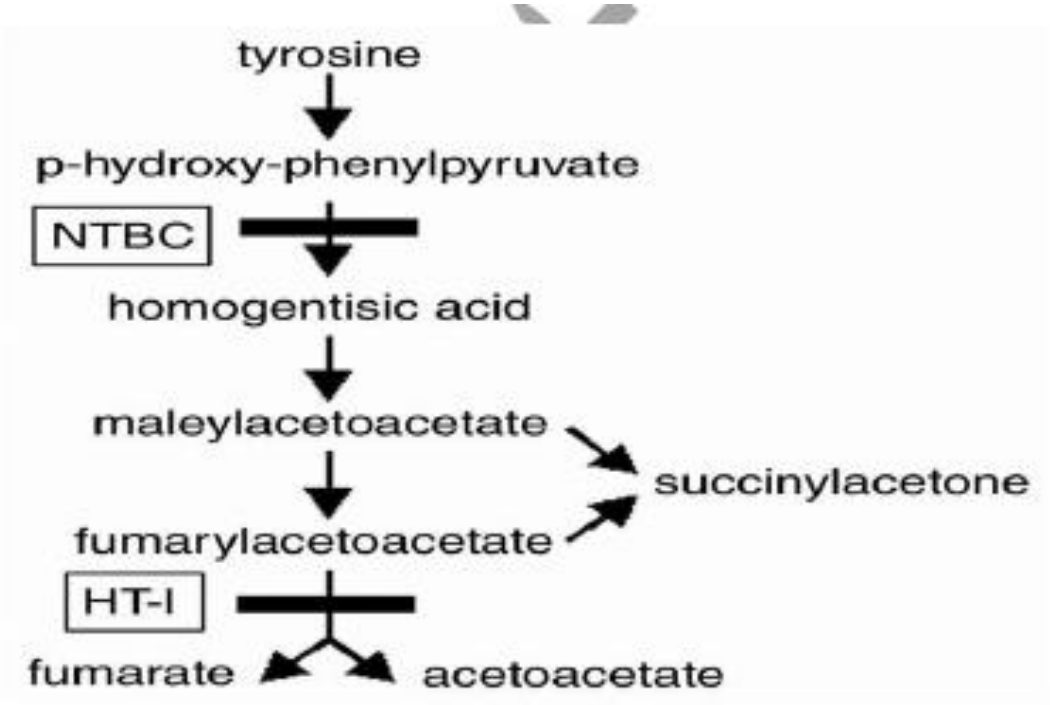
• Diagnosis may involve measuring the phenylalanine concentration in blood taken from a heel prick.

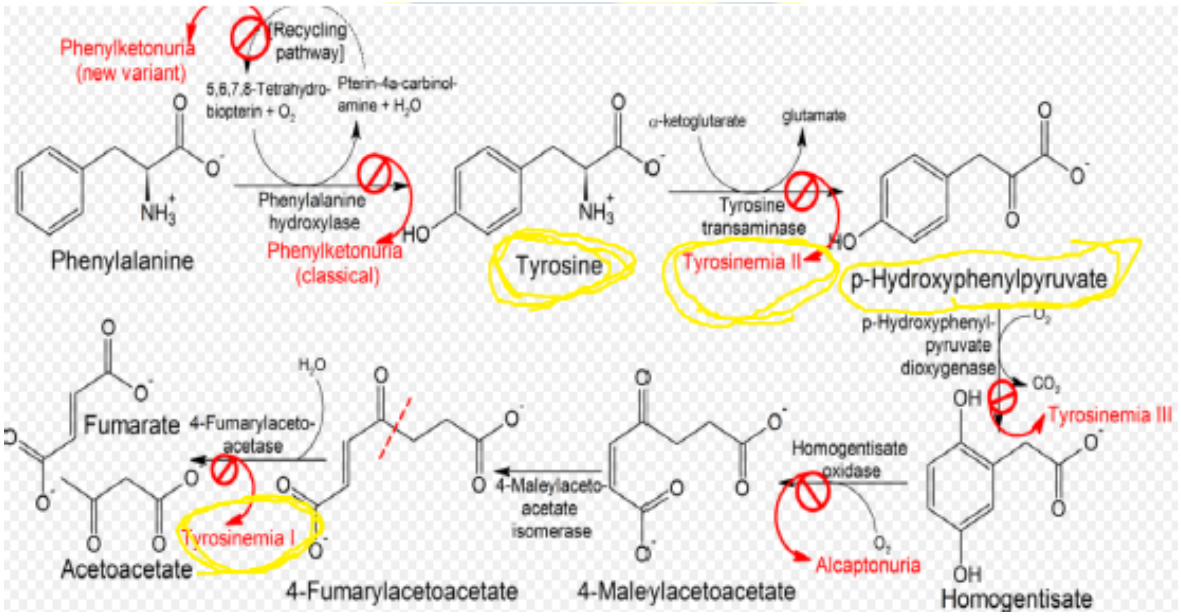
Infants who are exposed in utero to the high phenylalanine concentrations of undiagnosed or poorly controlled phenylketonuric

Tyrosinaemia: renal tubular dysfunction, hypoglycaemia and severe liver disease with very raised plasma alkaline phosphatase

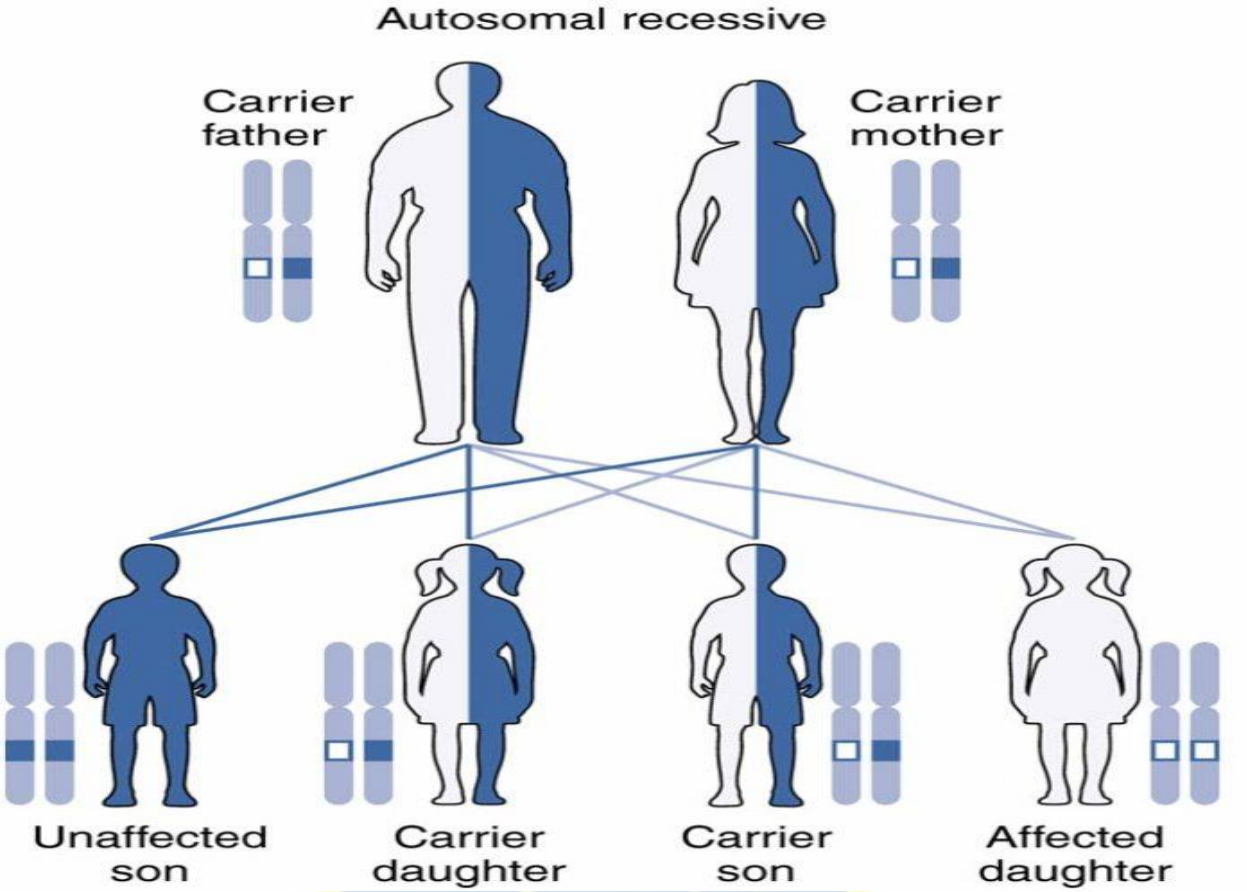
concentration. The defect is due to abnormal fumarylacetoacetase leading to raised tyrosine, succinylacetone and hydroxyphenylpyruvate

Treatment can be dietary, by liver transplantation or by nitro-trifluoro methylbenzoyl cyclohexanedione, which is thought to reduce the accumulation of some of the toxic metabolites.





Alkaptonuria:



• Alkaptonuria is an autosomal recessive disorder associated with a deficiency of homogentisic acid oxidase. Homogentisic acid accumulates in tissues and blood, and is passed in the urine.

• Oxidation and polymerization of homogentisic acid produce the pigment alkapton, in much the same way as polymerization of dihydroxyphenylalanine results in melanin.

• The deposition of alkapton in cartilages, with consequent darkening, is called ochronosis and results in visible darkening of the cartilages of the ears and often arthritis in later life.

Albinism:

• A deficiency of tyrosinase in melanocytes causes one form of albinism; it is inherited as an autosomal recessive disorder.

• Pigmentation of the skin, hair and iris is reduced and the eyes may appear pink. Reduced pigmentation of the iris causes photosensitivity, and decreased skin pigmentation is associated with an increased incidence of certain skin cancers.

• The tyrosinase involved in catecholamine synthesis is a different isoenzyme, controlled by a different gene; consequently, adrenaline (epinephrine) metabolism is normal.

Homocystinuria:

• Homocystinuria is an autosomal recessive disorder due to deficiency of cystathionine synthase.

• These pathways involve sulphur-containing amino acids. Patients may show progressive central nervous system (CNS) dysfunction, thrombotic disease, eye disease, including cataracts, and cardiovascular problems.

• The diagnosis of homocystinuria is based on the presence of raised urinary and plasma homocysteine with low plasma methionine concentrations. The defective enzyme can be assayed in cultured skin fibroblasts.

Histidinaemia:

• Histidinaemia is associated with deficiency of histidinase, an enzyme needed for normal histidine metabolism, and is probably inherited as an autosomal recessive trait.
• Some individuals may have intellectual disabilities and speech defects, but others may be normal.

Maple syrup urine disease:

• In maple syrup urine disease, which is inherited as an autosomal recessive condition, there is deficient decarboxylation of the oxoacids resulting from deamination of the three branched-chain amino acids, leucine, isoleucine and valine.
• These amino acids accumulate in the plasma and are excreted in the urine with their corresponding oxoacids

Inherited disorders of amino acid transport mechanisms:

● *the dibasic amino acids* (with two amino groups) cystine, ornithine, arginine and lysine (cystinuria) ● *many neutral amino acids* (with one amino and one carboxyl group) (Hartnup's disease), ● *the imino acids* proline and hydroxyproline, which probably share a pathway with glycine (familial iminoglycinuria).

Amino aciduria:

• Amino acids are usually filtered by the glomeruli, reach the proximal tubules at concentrations equal to those in plasma and are almost completely reabsorbed as they pass through this part of the nephron.
• Amino aciduria may therefore be of two types. ● *Overflow amino aciduria* In which, because of raised plasma concentrations, amino acids reach the proximal tubules at concentrations higher than the reabsorptive capacity of the cells. ● *Renal amino aciduria* In which plasma concentrations are low because of urinary loss due to defective

tubular reabsorption.

Cystinuria:

• Cystinuria is the result of an autosomal recessive inherited abnormality of tubular reabsorption, with excessive urinary excretion, of the dibasic amino acids cystine, ornithine, arginine and lysine.
• A similar transport defect has been demonstrated in the intestinal mucosa, but, although dibasic amino acid absorption is reduced, deficiencies do not occur because they can be synthesized in the body.
• Cystine is relatively insoluble and, because of the high urinary concentrations in homozygotes, may precipitate and form calculi in the renal tract.
• In heterozygotes, increased excretion can be demonstrated, but concentrations are rarely high enough to cause precipitation. The diagnosis of cystinuria is made by demonstrating excessive urinary excretion of the characteristic amino acids

Cystinosis:

• This is a very rare but serious disorder of cystine metabolism, characterized by intracellular accumulation and storage of cystine in many tissues.
• It must be distinguished from cystinuria, a relatively harmless condition. Renal tubular damage by cystine causes Fanconi's syndrome. Amino aciduria is non-specific and of renal origin. Affected individuals may die young.

Hartnup's disease:

• Hartnup's disease is a rare autosomal recessive disorder in which there are renal and intestinal transport defects involving neutral amino acids.
• Many of the clinical manifestations can be ascribed to reduced intestinal absorption and increased urinary loss of tryptophan.

• The clinical features of Hartnup's disease are intermittent and resemble those of pellagra, namely a red, scaly rash on exposed areas of skin, reversible cerebellar ataxia and mental confusion of variable degree.
• Despite the generalized defect of amino acid absorption, there is no evidence of protein undernutrition; this may be because intact peptides can be absorbed by a different pathway.
• Excessive amounts of indole compounds, originating from bacterial action on unabsorbed tryptophan, are absorbed from the gut and excreted in the urine.

Familial iminoglycinuria:

• Increased urinary excretion of the imino acids proline and hydroxyproline, and of glycine, despite normal plasma concentrations, is due to a transport defect for these three compounds. The condition is inherited as an autosomal recessive trait.

3 Lysosomal disorders:

1-The mucopolysaccharidoses

The MPSs are rare conditions caused by defects of any of the several enzymes that hydrolyse mucopolysaccharides (glycosaminoglycans), which therefore accumulate in tissues such as the liver, spleen, eyes, CNS, cartilage and bone.
***A- Hurler's syndrome* (MPS IH)** is the least rare in infancy or early childhood short stature, intellectual disabilities and clouding of the cornea. They usually die young of cardiorespiratory disease.
B- Scheie's syndrome (MPS IS) is difficult to distinguish clinically from Hurler's but has a much better prognosis; there is little intellectual disability.
***C- Hunter's syndrome* (MPS II),** in contrast to all the other MPSs, is inherited as a sex-linked recessive trait.
D- Sanfilippo's syndrome, which manifests severe CNS abnormalities, and

E- Morquio's syndrome, which is associated with short stature, barrel chest, genu valgum and other skeletal abnormalities.

The MPSs can increased urinary excretion of sulphated glycosaminoglycans, such as dermatan, heparan and keratan sulphates,

2-Lipid storage disorders; deficiency of a lysosomal hydrolase is inherited, resulting in the accumulation of sphingolipid.

- GM1 gangliosidosis defect of b-galactosidase,
- GM2 gangliosidosis such as Tay–Sachs disease, due to hexosaminidase deficiency,
- Gaucher's disease, due to a deficiency of b-glucosidase (glucocerebrosidase),
- Niemann–Pick disease, resulting from sphingomyelinase deficiency,
- Fabry's disease, resulting from a-galactosidase A deficiency,
- metachromic leucodystrophy, resulting from arylsulphatase deficiency.

Clinical features of these conditions may include organomegaly, skeletal abnormalities, pulmonary infiltration and cherry-red macular spot on ophthalmologic examination

4 Carbohydrate disorders: Disorders of sugars

• Galactosaemia is an autosomal recessive disorder due to galactose-1-phosphate uridyl transferase (Gal-1-PUT) deficiency.

• Galactose is necessary for the formation of cerebrosides, of some glycoproteins and, during lactation, of milk. Excess is rapidly converted into glucose.

Tubular damage may cause a generalized amino aciduria. The diagnosis is made by identifying galactose by thin-layer chromatography and by demonstrating a deficiency of Gal-1-PUT activity in erythrocytes.

Urinary reducing substances are usually positive provided the infant is on a lactose-containing milk diet. Treatment involves eliminating galactose in milk and milk products from the diet.

• Sufficient galactose for the body's requirements can be synthesized endogenously as uridyl disphosphate galactose.

The glycogen storage disorders:

• *Glycogen storage disease type I* This is known as von Gierke's disease and is a deficiency of glucose-6-phosphatase. Patients may display a lactic acidosis, hypoglycaemia, hyperuricaemia and hypertriglyceridaemia.

• *Glycogen storage disease type II* Pompe's disease or maltase deficiency (α-1,4- glucosidase) is a lyosomal defect. It is associated with skeletal myopathy, including muscular hypotonia and cardiomyopathy.

• *Glycogen storage disease type III* This is a defect of debranching enzyme and is known as Forbes–Cori disease.

Glycogen storage disease type IV : defect of glycogen branching enzyme and is also called Andersen's disease

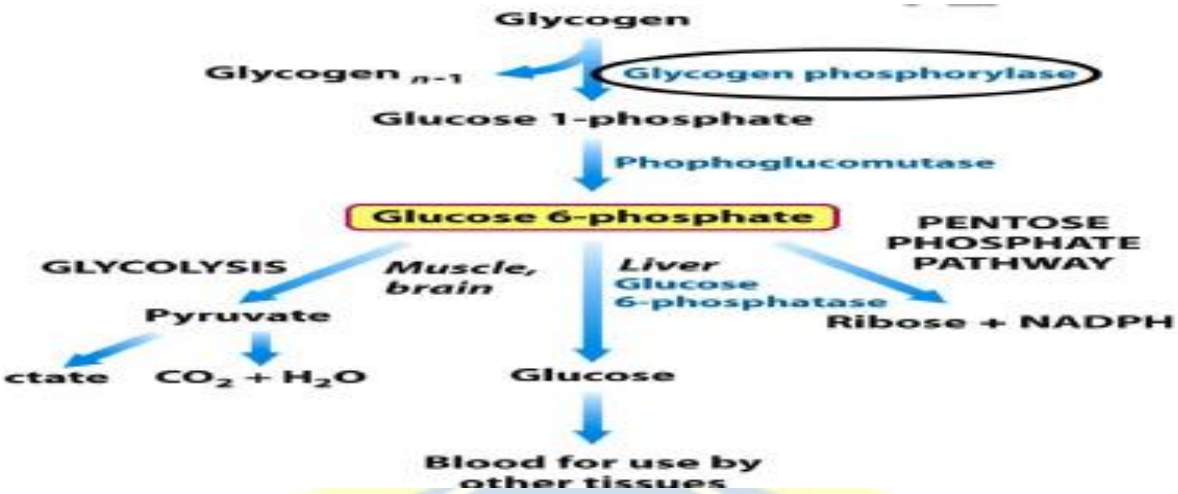
Glycogen storage disease type V ; McArdle's disease is a deficiency of muscle phosphorylase. Muscle cramps and fatigue occur on heavy exertion.

Glycogen storage disease type VI

Hers' disease is due to hepatic phosphorylase deficiency. Symptoms may be mild, although growth retardation may occur.

Glycogen storage disease type VII

Tarui's disease is due to phosphofructokinase deficiency. The symptoms are similar to those of type V.



5 Lipid disorders and organic acid urias:

Those organic acids derived from the metabolism of amino acids, carbohydrates and lipids are often detectable in the urine; others accumulate if there is an enzyme deficiency in a specifi c metabolic pathway.

• Examples include methylmalonic acidaemia, glutaric acidaemia, isovaleric acidaemia and proprionic acidaemia. These disorders, known as organic acidurias, are individually rare, but collectively have an incidence of about 1 in 12 000 births, similar to that of PKU.

• They may present in the neonatal period with life-threatening metabolic acidosis, vomiting and hypotonia, or in early infancy with failure to thrive, a Reye-like syndrome and convulsions associated with profound hypoglycaemia. They may also be a cause of sudden infant death.

Mitochondrial disorders:

• Mitochondrial DNA (mtDNA) is derived from the mother This differs from nuclear DNA in that there are no introns and the mutation rate is thus about 10–100 times greater than that of nuclear DNA.

Mitochondria lack an adequate DNA repair mechanism. A number of clinical features may be present, including neuropathy, intellectual disabilities, lactic acidosis, myopathy, ocular defects, diabetes mellitus, anaemia and hearing loss.

7 Peroxisomal disorders:

• In this group of disorders there is either a deficiency of a peroxisomal enzyme or a defect in forming intact peroxisomes.

described: defects of phytanic acid oxidation (Refsum's disease), dihydroxyacetone phosphate acyltransferase abnormality (Zellweger's syndrome), catalase defects

8 Drugs and inherited metabolic disorders:

• Disorders resulting in deficient metabolism of a drug The muscle relaxant suxamethonium (succinyl choline, or scoline) normally has a very brief action because it is rapidly broken down by plasma cholinesterase. In suxamethonium sensitivity, a cholinesterase variant of low biological activity impairs the breakdown of the drug, and prolonged postoperative respiratory paralysis may result ('scoline apnoea').

Disorders resulting in an abnormal response to a drug:

• Deficiency of glucose-6-phosphate dehydrogenase (G6PD) may cause haemolytic anaemia, and is relatively common in ethnic groups of Mediterranean origin.

• It is X-linked. This enzyme catalyses the first step in the hexose monophosphate pathway and is needed for the formation of nicotinamide adenine dinucleotide phosphate, which is important for the maintenance of intact red cell membranes. Numerous variants of G6PD deficiency have been described. Haemolysis may be precipitated by certain antimalarial drugs, such as primaquine, and by sulphonamides. In the inherited hepatic

9- **Miscellaneous disorders**

There are many other IEMs in addition to those mentioned above, including congenital adrenal hyperplasia , adenosine deaminase deficiency, electron transport chain defects and sulphite oxidase deficiency